COMPARISON OF MISOPROSTOL AND MISOPROSTOL WITH ISOSORBIDE MONONOTRATE IN SECOND TRIMESTER TERMINATION OF PREGNANCY

Dissertation Submitted to the

THE TAMILNADU Dr.M.G.R.MEDICAL UNIVERSITY
CHENNAI

In partial fulfillment
Of the requirement for the degree of

M.S OBSTETRICS AND GYNECOLOGY
BRANCH II

MADRAS MEDICAL COLLEGE
CHENNAI TAMILNADU

APRIL 2016

CERTIFICATE

This is to certify that this dissertation entitled **"COMPARISON OF MISOPROSTOL AND MISOPROSTOL WITH ISOSORBIDE MONONOTRATE IN SECOND TRIMESTER TERMINATION OF PREGNANCY"** has been done by Dr.Rukkayal Fathima.P, Post Graduate in M.S (Obstetrics and Gynaecology) under my overall supervision and guidance at Govt. Hospital for Women and Child Health, Institute of Obstetrics and Gynaecology, Madras Medical College, Chennai in partial fulfillment of regulations of TamilNadu Dr.M.G.R. Medical University for the award of M.S. Degree in Obstetrics and Gynecology.

Prof. Dr.J Sarala , M.D; DGO,
Govt.Hospital for Women and
Child Health,
Institute of Obstetrics and
Gynaecology,
Madras Medical College, Chennai.

Prof. Dr. S.Baby Vasumathi, MD.,DGO.,
Director,
Institute of Obstetrics and Gynecology,
Madras Medical College,Chennai

Prof. Dr. R. Vimala
Dean,
Madras Medical College,
Chennai

DECLARATION

I Dr.Rukkayal Fathima.P solemnly declare that the dissertation titled **"COMPARISON OF MISOPROSTOL AND MISOPROSTOL WITH ISOSORBIDE MONONOTRATE IN SECOND TRIMESTER TERMINATION OF PREGNANCY"** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other person for any award, degree or diploma to any other university board either in India or abroad.

This is submitted to The Tamil Nadu Dr. MGR Medical University, Chennai in partial fulfillment of the rules and regulations for the award of M.S degree Branch II Obstetrics and Gynecology to be held in March 2016

PLACE: **Dr. Rukkayal Fathima . P**

DATE

ACKNOWLEDGEMENT

I am very thankful to **Prof. Dr. R. Vimala M.D.,** Dean, Madras Medical College for her kind permission to carry out this study at Institute of Obstetrics and Gynaecology, Chennai.

I express my sincere gratitude and thanks to **Prof.Dr.S.Baby Vasumathy,M.D.,D.G.O.,** Director, Institute of Obstetrics and Gynecology, Chennai for her guidance.

It is a genuine pleasure to express my deep sense of gratitude and thanks to my Guide, **Prof. Dr.J Sarala M.D.,D.G.O.** for her encouragement and guidance in conducting the study.I am indebted to acknowledge that without her support ,this study could not have been completed.

I am very grateful to **Prof . Dr. Prema ElizabethM.D.,D.G.O , Chief , Department of Family welfare** for providing me access to the patients of Department of Family Welfare and helping me in conducting my studies

I am thankful to my Co-Guide **Assistant Professor Dr. Thangamani M.D.,** IOG,Chennai for her valuable guidance and suggestions.

My sincere thanks to all other Assistant Professors and fellow postgraduates for their help during the course of this study. Lastly and most importantly, I am indebted to all my patients who willingly participated in this study.

CONTENTS

INTRODUCTION

INTRODUCTION

DEFINITION

Abortion is the termination of pregnancy by the removal or expulsion of the foetus or embryo from the uterus before the age of viability, resulting in or caused by its death (WHO 2009).

An abortion can be spontaneous or induced. ***A spontaneous abortion*** is beyond the patient's control and it takes place due to complications of pregnancy. ***An induced abortion*** can be therapeutic abortion or elective abortion. ***Therapeutic abortion*** is an abortion induced to preserve the heath of the pregnant female while an ***elective abortion*** is the abortion done for any other reason.

The term abortion mostly refers to induced abortion of pregnancy, while spontaneous abortions are usually termed as miscarriages.

MIDTRIMESTER ABORTION

Second trimester, or mid trimester ranges from ***12-28 weeks*** of gestation.It is further divided into an early period between 12 and 20 weeks and a late period between 20 and 28 weeks.

Mid-trimester abortion constitutes 10-15% of induced abortions. Due to the wide spread use of prenatal diagnostic techniques, detection of serious fetal anomalies is on the rise. This has led to a drastic increase in the second trimester induced abortions.Medical methods of induced abortions in the midtrimester has shown considerable development and have proven to be safe and accessible.

The incidence of induced abortion is around 22%. (i.e. more than 46 million of 210 million pregnancies in a year result in induced abortions). Second trimester pregnancy termination has been reported to be associated with 3-5 times increased morbidity and mortality risks when compared to the first trimester termination of pregnancy.

REPRODUCTIVE RIGHTS

It is the basic right of every couple and individual to decide on the number, spacing and timing of their children.They must have adequate information and means to exercise their right.It is their right to attain the highest standard of sexual and reproductive health. It is also the right of the individual to make decisions regarding reproduction without any discrimination, violence and coercion.

Every woman has a right to her private life. This has been the basis on which the government has emphazised and upheld the right of a woman to have an abortion. Every woman has the right to access abortion.This is based on her right to decide on the number and spacing of her children. The right of women to receive information about abortion options is based on the right to freedom of expression.

LEGAL ISSUES

Indian law allows abortion; if the continuation of pregnancy would endanger the life of the pregnant women or cause serious injury to her physical or mental health.The Indian Medical Termination Of Pregnancy Act has made termination of pregnancy legal.It has certain conditions to safeguard the mental and physical health of the mother.

The supremem court has emphasised that right of a woman to her private life is implicit according to ***Article 21*** of the Constitution.Her right to abortion is based on this article.

INDIAN MEDICAL TERMINATION OF PREGNANCY ACT, 1971

In India, ***Shantilal Shah Committee (1964)*** recommended liberalization of abortion law in 1966 to reduce maternal mortality and morbidity associated with illegal abortions. On this basis, 1969 MTP bill was introduced in Rajyasabha and Loksabha and passed by Indian Parliament in August 1971. The Medical Termination of Pregnancy Act (MTP Act) was implemented from April 1972. The implemented rules and regulations were again revised in 1975 to eliminate time consuming procedures for approval of places and to make services more readily available.

A registered medical practitioner (RMP) is protected under law if pregnancy is terminated in accordance with ***Section 3*** of the MTP Act which emphasises the importance of the legal consent.

INDICATION FOR TERMINATION OF PREGNANCY:

There are four grounds based on which MTP can be performed.

1) **MEDICAL GROUNDS**
2) **EUGENIC GROUNDS**
3) **HUMANITARIAN GROUNDS**
4) **SOCIAL GROUNDS**

MEDICAL GROUNDS

Medical grounds when the continuation of pregnancy is likely to:

1) Endanger the life of the pregnant women or
2) Cause grevious injury to her physical and/or mental health as in case of severe hypertension ,cardiac disease ,diabetes, psychiatric illness ,genital cancer ,breast cancer,etc.

EUGENIC GROUNDS

Eugenic grounds when there is a substantial risk of the child being born with serious physical or mental abnormalities.

Eg ; hereditary disorders, congenital malformations ,etc..

HUMANITARIAN GROUNDS

Humanitarian grounds when the pregnancy is caused by rape or incest.

SOCIAL GROUNDS

Social grounds when

1) Pregnancy resulting from failure of contraceptive device or method.
2) When in actual or reasonably foreseeable future , her environment might lead to risk or injury to her health.

Abortions on demand are not permitted by the MTP act. It is the medical

practitioners responsibility to opine regarding the presence of valid legal indication. These indications are also mandatory even in medical methods.

VALID LEGAL CONSENT:

1. Written consent of the guardian is mandatory in case of termination of pregnancy in minors (under 18 years) and lunatics (according to section 3 of **Indian lunacy act 1912)**
2. In adult women over 18 years, termination of pregnancy is permissible with her valid written consent.

Rule 8 of MTP Rules recommends that the consent be informed and recorded in FORM C. The consent must be recorded every time an early abortion is carried out by medical method. In an adult woman, no other person's consent is required except her own.

THE PLACE WHERE MTP CAN BE PERFORMED

The act stipulates that no MTP can be performed at any place other than :

1. At hospital established or maintained by Government.
2. A place recognized and approved by the government , under this act.

QUALIFICATION OF THE PERSON WHO CAN PERFORM MTP

1. Postgraduate degree or diploma in Obstetrics and Gynecology
2. Registered before commencement of the Act with minimum 3 years experience in Obstetrics and Gynaecology
3. Registered after commencement of the Act if:
    - Assisted in minimum 25 MTPs in a government hospital or a training institute recognised by the government.
    - Six months of house surgeon ship in Gynaecology and Obstetrics
    - Experience in any hospital of over 1 year in the field of Gynaecology and Obstetrics.
    - For pregnancies which have exceeded 12 weeks but is within 20 weeks of gestation, opinion of two registered medical practitioners is necessary

METHODS OF ABORTION ACCORDING TO GESTATIONAL PERIOD

LENGTH OF AMENORRHOEA	TECHNIQUE
TILL 9 WEEKS	• Anti-progestins or prostaglandins • Vacuum aspiration
9 – 14 WEEKS	Vacuum aspiration (with Cervical priming after 12 weeks and in nulliparous women)

MORE THAN 14 WEEKS	• Antiprogestins + prostaglandins
	• Prostaglandins alone
	• D & E (with cervical preparation)
	• NOT USED
	  ○ Hypertonic saline ,Urea
	  ○ Ethacridine lactate

METHODS OF SECOND TRIMESTER ABORTION

OUTDATED TECHNIQUES

The commonly used methods of early 1970s which are outdated now are :

Intra-Amniotic instillation of drugs:

- 20% Hypertonic saline
- Hypertonic glucose
- Urea
- Prostaglandins

Extra-Amniotic instillation of drugs:

- 0.1% Ethacridine Lactate (Rivanol)
- Hypertonic saline
- Prostaglandins
- Mifepristone and Misoprostol

Extra Uterine methods:

- I.M. $PGF_{2\alpha}$
- I.V./I.V oxytocin

Extra-Amniotic insertion of devices:

- Sterile catheters

Surgical methods:

- Dilatation and Evacuation
- Aspirotomy and Hysterotomy.

Drawbacks of these methods:

- The intra amniotic space had to be punctured in many methods.
- Foley catheter was introduced into the extra amniotic space
- The induction to abortion interval was relatively long
- There was a need for curettage after the expulsion of fetus
- Hypertonic saline had the risk of causing disseminated intravascular coagulation.

Medical abortion methods have low morbidity. Recently is has become better accessible.

MEDICAL TERMINATION OF PREGNANCY

Medical abortion, being simple safe and effective and without risk of invasive procedures and anaesthesia is becoming method of choice in many centres and has successfully replaced surgical termination of pregnancy; the success rate is also high as 95 %.

The management of second trimester abortion changed with the advent of prostaglandin analogues. The subsequent introduction of Anti-progestin, Mifepristone, shortened the induction abortion interval and reduced the dosage of Misoprostol required, though the cost of Mifepristone and Misoprostol combination is still high and is not affordable by many in a resource poor setting.

The following strategies can be adopted to make medical abortions safer and easily feasible in India.

1. Continue Clinical / Acceptability studies:

It enables the provider know if the woman likes the method and also helps the provider to gain experience.

2. Conduct Non-Clinical studies:

It is a research done to record the experience of the women and to assess knowledge of the provider.

3. Increase provider knowledge:

New training centres for medical abortion should be established

- Training for medical abrortion should be incoporated into the already existing MTP courses.

- The national guidelines should be made flexible to facilitate adoption on evidence based regimen.

4. Increase client knowledge:

The client knowledge can be improved by media outlets, magazines, talk shows, school health talks.

5. Document serious adverse effects:

The registered MTP provider must report any serious adverse event during the monthly MTP reporting.

METHODS OF MEDICAL TERMINATION OF PREGNANCY

PRINCIPLE

Cervical ripening done prior to surgical termination of pregnancy reduces the cervical injury and other operative morbidity. Prostaglandin analogues induce cervical ripening in two ways. By acting directly on the cervix and by stimulating myometrial activity concomitantly.The prostaglandin receptors are present throughout the pregnancy so they play a significant role in the regulation of uterine contractility and their analogues are effective for termination of pregnancy. Naturally occurring prostaglandins are potent stimulants of uterine contractility and they cause ripening and dilatation of the cervix.

DRUGS USED

CARBOPROST

Carboprost (15 (S)-15-methyl $PGF_{2\alpha}$) was one of the first prostaglandin analogue to be tested clinically for second trimester abortion. It can be used intra amniotically or given I.M. It is associated with high incidence of gastro intestinal side effects. So it is not used as the method of choice for medical abortion. It can be used if other methods fail.

SULPROSTONE

Sulprostone (16 phenoxy-ω-17, 18, 19, 10-tetranor PGE_2 methyl sulphonylamide) was used in the 1980s for the second trimester abortions. It caused myocardial infarction and other cardiovascular complications due to coronary vasospasm which led to its withdrawal from the market.

GEMEPROST

Gemeprost is a PGE_1 analogue and is used as a vaginal pessary. It has been used for ripening and dilating the cervix before vacuum aspiration in late first trimester and early second trimester termination of pregnancy. It is a well established method of second trimester abortion and is more effective when compared to intra-amniotic carboprost or extra-amniotic or intra cervically administered PGE_2.

MISOPROSTOL

Misoprostol is a ***synthetic PGE_1 analogue*** (15-deoxy-16-hydroxy-16 - methyl PGE_1), which was initially developed for the prevention and treatment of peptic ulcer. Misoprostol is manufactured as 100 and 200 microgram and can be used as orally, rectally and vaginally.

PHARMACOLOGY:

Following oral administration of this drug ,it gets absorbed quickly and de-esterised to its active pharmacological form misoprostol acid. Concentration of this metabolite reaches its peak in plasma by 30 minutes and declines rapidly with a half life of 20 minutes. Primary site of metabolism of this drug is in liver and less than 1 percent of this metabolite is excreted in urine. Dose of the drug needs adjustment when used in patients with liver disease whereas it is not required in patient with renal disease and not on dialysis. Misoprostol does not affect hepatic mixed function oxidase (Cytochrome P-450) enzyme system.

Vaginal administration has the advantage of reducing gastrointestinal side effects and exerts profound effect on reproductive tract. After application in the posterior fornix, plasma concentration reaches peak by one to two hour and then slowly declines.

After oral and vaginal administration of this drug, intrauterine pressure begins to increase by 8 and 25 minutes and reaches maximum by 25 and 46 minutes respectively. When compared with oral administration,vaginal misoprostol caused significantly higher level of maximum uterine contractility. Cumulative dose up to 2200 mg has been found to be tolerated by expectant mothers with no serious side effects when administered over 12 hours. Misoprostol has long lasting action following vaginal administration than sublingual and oral route.

SIDE EFFECTS

Side effects of misoprostol are dose dependant.They are

- nausea
- vomitting
- diarrhoea
- abdominal pain
- chills
- shivering and fever . Myocardial infarction and bronchospasm has not been reported yet with the drug.

TERATOGENICITY

Ingestion of misoprostol in the first trimester in an unsuccessful effort to induce abortion causes **congenital facial paralysis (moebius syndrome) and limb defects** in the infants.

In a recent case control study, malformations like

- Transverse limb defects
- Ring shaped constriction of extremities
- Arthrogryposis
- Hydrocephalus
- Holoproscencephaly
- Exstrophy of the bladder has been reported in infants.

MIFEPRISTONE or RU-486

It is the anti-progestin approved for use in termination of pregnancy. This drug helps in two ways:

1. By causing cervical dilatation and reducing its resistance to dilatation
2. By increasing the sensitivity of uterus to exogenous prostaglandinds and thus shorten the induction abortion interval, increase the successful termination of pregnnancy and reduce the total dose of PG required.

NITRATES

Human studies have shown that nitric oxide donors are effective in ripening the cervix in first trimester abortions before suction evacuation of the uterus, though they are less effective than prostaglandin analogues. However they are more acceptable to patients as the side effects of nitric oxide donors are lower when compared to prostaglandin analogues.

Nitroglycerine was first synthesised in ***1846*** by ***Sobrero*** who observed that a small quantity of oil substance placed on tongue elicited a severe headache. Based on this evolved other organic nitrates like amylnitrates, isosorbide dinitrate, isosorbide mononitrate, erthrityl tetranitrate. The empirical observation was that they could be safely used for the rapid, dramatic relief of symptoms of angina pectoris led to their wide spread use by medical professionals.

CHEMISTRY

They are ***polyol esters*** of nitric acid. Nitrate esters are characterised by C–O–N O_2 (Carbon- Oxygen-Nitrogen) compounds. They are high molecular mass nitrate esters and are in solid form. The fully nitrated polyols are lipid soluble whereas incompletely nitrated metabolites are more soluble in water. They are capable of denitration to release Nitric Oxide (NO). Hence they are called ***Nitro Vasodilators.***

MECHANISM OF ACTION

When Nitric Oxide (NO) is released by denitration into the smooth muscle cell it activates the Guanylate Cyclase in vascular smooth muscle cells and converts GTP (Guanosine Triphosphate) to cGMP (Cyclic Guanosine Monophosphate) and increase intracellular cGMP levels. This cGMP in turn blocks the conversion of Myosin light chain kinase to phosphorylated Myosin light chain kinase which is helping in contraction of smooth muscles. Also cGMP blocks the entry of calcium into the cell thereby causing smooth muscle relaxation.

PHARMACOKINETICS

Nitric oxide (NO) is a simple free biologically active radical gas, soluble in both water and lipid and therefore freely diffusible in cell environment. Nitric oxide is synthesized from the amino acid L–Arginine, has a short half life (approximately 4 seconds) and it is not stored in vivo. The synthesis of NO is regulated by NO synthases (NOS) of which three isoforms are identified: inducible NOS (iNOS), endothelial NOS (eNOS) and neuronal NOS (nNOS).

Nitric oxide synthases require calcium / calmodulin for activation Nitric oxide is rapidly converted to the final metabolites nitrate and nitrite. This reaction is catalyzed by transition metals including iron. The half life of NO and the ratio of nitrate and nitrite in aqueous solutions, depend upon surrounding conditions i.e., presence of oxygen-derived radicals, pO_2, pH and concentrations of transition metals and thiols. Nitric oxide is a mediator in many biological processes such as inflammation, immune response, smooth muscle relaxation, vascular homeostasis and neurotransmission.

In the female reproductive tract NO is involved in ovulation, tubal transport, implantation, pregnancy maintenance, labor and delivery.Since they are lipid soluble, they are well absorbed from buccal mucosa, intestines and skin. On oral route they are denitrated by glutathione reductase. Duration of action depends on the rate of absorption from the site of administration and the rate of metabolism.

Isosorbide Mononitrate is an active metabolite of Isosorbide Dinitrate.It undergoes little first pass metabolism when administered orally.So Bioavailability is high. Inter individual differences are minimal and longer acting ($T_{1/2}$ 4- 6 hours). The low rate of side effects when administered vaginally reflects the first uterine pass effect and its high uterine and low serum concentrations.

ADVERSE EFFECTS:

There are no documented side effects of nitric oxide when administered vaginally.Side effects of nitric oxide when given through other routes are:

- Headache
- Dizziness
- Palpitation

These are mostly due to vasodilatation.

COMPLICATIONS ASSOCIATED WITH MTP:

Usually only illegal abortions are considered unsafe abortions. But complications can occur in any induced abortions. These complications depend upon the following conditions.

- Patient's pre-abortal health status
- Gestational age of the foetus
- Person who provides MTP
- Facilities available in the MTP centre

MORTALITY

- Below 8 weeks pregnancy is 0.5%
- 9-12 weeks pregnancy is 1.6%
- 11-12 weeks pregnancy is 3.3%
- Risk increases by 50 % per week of gestation

Common causes of maternal morbidity and mortality are

1.	Uterine haemorrhage	1-4%
2.	Cervical injury	0.01-1%
3.	Uterine perforation	0.1-0.28%
4.	Injury to bladder and intestines	0.05 – 0.1%

OTHER COMPLICATIONS:

1. Retained products
2. Continuation of pregnancy
3. Pelvic cellulitis
4. Pelvic abcess
5. Tubo ovarian mass
6. Pelvic thrombophlebitis

SERIOUS COMPLICATIONS

1. Anaesthetic reactions
2. Embolic events
3. Hemorrhage
4. Infection
5. Septicemia
6. Peritonitis
7. Endotoxic shock
8. Tetanus
9. Acute renal failure
10. DIVC

LATE COMPLICATIONS:

1. Infertility
2. Ectopic pregnancy
3. Recurrent abortions
4. Premature deliveries
5. Cervical incompetence
6. Rh isoimmunisation
7. Asherman’s syndrome
8. Placenta previa
9. Adherent placenta
10. Rupture of uterus during pregnancy and labour

.

REVIEW OF LITERATURES

REVIEW OF LITERATURES

1) **METHODS OF ABORTION**
2) **MISOPROSTOL**
3) **MIFEPRISTONE**
4) **NITRATES**

METHODS OF ABORTION

The earliest available information regarding mid trimester abortion is with the usage of quinine and ergot preparations dating back to 17th century , they being abandoned because of almost 100% failure. Although a very good adjuvant to other methods of abortion oxytocin itself in high concentration is not effective because the uterus is not so sensitive to it as it is so towards term.

From 1946 – 1952 in Japan and United States from 1960 and in India from 1970 hypertonic saline (20% NaCl) came into vogue as a safe and effective method. The induction-abortion interval is between 22 – 39 hrs with the success rate of 80 %. However there were complications noted in the form of hemorrhage, infection, hypernatremia and inadvertent intravascular injections leading to coma, convulsion and death. Hypertonic saline has a 0.8% risk of causing disseminated intravascular coagulation. This is because hypertonic saline may get absorbed into

the intravascular compartment after an inadvertent intramuscular injection or intraperitoneal injection or from the amniotic cavity. This may lead to hypernatremia and necrosis of the affected tissues.

Utus Paste (semi solid soap mixed with potassium iodide and astringents) instilled in extra-amniotic space was introduced in 1968 and abandoned in 1974 due to high failure and infection. In 1971 urea solution in strength of 40 – 60% was used intra amniotically with an average induction abortion interval of 44-51 hrs. Urea alone is not ideal abortifacient needing back up with PGF2 alpha analogues. With improved methods being available the use of urea as an abortifacient drug has been given up.

Rivanol is a dye with antiseptic properties. It is less toxic than hypertonic saline. Rivanol causes chemical trauma to the fetal membranes and decidua, which stimulates endogenous PG and thromboxane production resulting in cervical ripening and initiating labour. The induction abortion interval ranges from 25 to 40 hrs .This could be reduced to 15 -20 hrs when oxytocin was used simultaneously. Oxytocin can cause serious side effects like water intoxication during I.V infusion.

Later in 1974 intrauterine instillation of glucose and mannitol were introduced but abandoned because of high failure rates and high incidence of infection.

SURGICAL METHODS:

Vacuum aspiration and dilatation and evacuation:

Vacuum aspiration is the surgical method used for first trimester termination of pregnancy. This procedure involves emptying of the uterus with a suction curette and blunt forceps. This procedure can also be used during the early second trimester. The risk of complications increases with advancing gestational age.

There is a 15 – 30% increase in the risk of major complications with each week of delay beyond 8 weeks of gestation. In between 12 and 15 weeks of gestation it is the clinician's decision regarding the method of abortion based on his skill and experience. Abortion above 12 weeks of gestation should be taken up by the senior staff member. Suction evacuation can be used for abortions upto 15 weeks of gestation without need of specialized instruments if the clinician has sufficient expertise in it.

The complications can be reduced by prior cervical priming and dilatation. Cervical trauma during surgical abortion is found to be less than 1%. The rate is lower when abortions are performed by experienced professionals and done early in pregnancy. The WHO and RCOG recommends '***cervical priming*** to be done before surgical method of abortion for pregnancy over 9 weeks for nulliparous

women, for women younger than 18 years of age, and for all women with pregnancy more than 10 weeks. Mechanical dilatation, Laminaria tents, PG analogues or mifepristone can be used to produce cervical dilatation. PG analogues are found to be safer for cervical dilatation than mechanical methods and laminaria tents. Duration of treatment determines the degree of cervical dilatation. Misoprostol and mifepristone combination has been shown to be effective for cervical priming before first trimester surgical abortion.

Gottileb et al 1991 conducted a study constituting 127 women at 13-14 weeks of gestation.There was no case of cervical injury or uterine perforation or recurettage during the study. The post abortion infection rate was 1.6%. The average amount of blood loss was 49ml (range 0-100ml), and only around 6 patients had blood loss >100ml. These results were similar when same procedure was used in the first trimester ,without any additional complications when PG analogues were used for pretreatment.

Dilatation and Evacuation:

Dilatation and evacuation (D&E) is the surgical method of choice at above 13 weeks of gestation. The suction evacuation is an appropriate method for between 12 and 15 weeks of gestation whereas D&E is the safe,convenient and effective method for above 15 weeks of gestation **RCOG (2004).** Safety and

efficacy of D&E for mid-trimester pregnancy termination by specialist practitioners is confirmed by the evidence available. D&E is found to be faster safer and more efficacious when compared to prostaglandins like PGF2alpha. Preoperative cervical priming reduces the cervical injury due to D&E in the second trimester.

Extra ovular placement of rubber tube was advocated by George (1979) for mid trimester abortion with prolonged induction – abortion interval being the major problem. Midtrimester abortion was induced with No.12 rubber catheter, 96% aborted within 40 hours

Saxena S.C and Sharma 1980 have studied termination of pregnancy using rubber catheter and Ryle's tube in 70 cases with 86.9% success rate.

PROSTAGLANDINS:

The term prostaglandin was coined by ***Van Euler*** in 1935 after he isolated a substance from the accessory glands of the male genital tract. Naturally occurring PGs like PGE_1, PGE_2, $PGF_{2\alpha}$ are effective stimulants of uterine contractility and it cause cervical priming and dilatation. The prostaglandin receptors are present throughout the pregnancy so they play a significant role in the regulation of uterine contractility and their analogues are effective for

termination of pregnancy. Naturally occurring prostaglandins undergo a rapid metabolism and is associated with high incidence of side effets. So it was replaced by prostaglandin analogues which was more suitable for clinical practice.

Gemeprost is a PGE1 analogue and is used as a vaginal pesssary. It has been extensively used as a non surgical method to dilate the cervix before VA in late first and early second trimester abortion.

The advent of PGs and PG analogues led to the improvement of medical abortion and there was a reduction in the risk for complications and side effects. Medical abortion further improved when mifepristone became available in the 1980s.

Mifepristone shortened the induction to abortion interval and reduced the requirement of dose of PG analogues. Nowadays medical abortion has become the method of choice in many countries.

SIDE EFFECTS OF PG ANALOGUES:

PGs have a stimulatory effect on the endometrium due to which it causes side effects like nausea, vomiting and diarrhea. Gemeprost is more frequently associated with diarrhoea whereas misoprostol causes fever. Some of the rare compications are uterine rupture, hemorrhage and cervical tear. Both misoprostol and gemeprost may cause uterine rupture rarely whether or not priming with mifepristone was done. In a women without previous scar the incidence of uterine rupture is around 0.1% - 0.2% in the second trimester termination of pregnancy using mifepristone and gemeprost. Prolonged retention of placenta is usually associated with major bleeding.

Mifepristone and misoprostol has reduced or eliminated the drawbacks of medical abortion with older methods like

- longer duration of labour,
- long hospital stay
- need for an invasive curettage

MISOPROSTOL

Misoprostol is a ***PGE_2 analogue***, produced and used since 1991 by ***Searle***, to prevent peptic ulcer disease induced by NSAIDS.***Von Euler*** (1935) found prostaglandins as an abortifacient.

Vaginally administered misoprostol has 3 times increased systemic biavailability when compared to orally administered misoprostol. In a comparative study of oral and vaginal misoprostol in the second trimester termination, 90% of vaginal group aborted in 48 hrs and 69% of the oral group aborted in 48 hrs. Vaginal pH does not appear to influence the efficacy of intravaginal misoprostol.

Misoprostol is over 70% effective in terminating pregnancy within 48 hrs when used in second trimester medical management of abortion. Misoprostol is uterotonic and provides an effective alternative to other methods of midtrimester termination.

A regimen using a combination of mifepristone 200mg and vaginal misoprostol (600-800 mcg as first dose) and oral misoprostol (400mcg every 3 hrs for 4 doses) gave the highest complete abortion rate (97%) and shortest induction abortion interval (6.5 hrs)

When mifepristone pretreatment was used before vaginal misoprostol, ,abortion rate was 90% in 24 hrs and induction abortion interval was 9 hrs.

In a randomized controlled trial to compare the effectiveness of 6 and 12 hrly administration of vaginal misoprostol for second trimester pregnancy termination, it was reported that misoprostol (600 mcg) administered at 12 hr

interval was associated with fewer adverse effects and was as effective as 6 hour interval and there was no significant difference in the mean induction to abortion interval at 6 hours (16hrs) and 12 hrs (16 hrs).

The efficacy of 400 mcg of tablet misoprostol inserted in the vagina every 12 hrs for a maximum of 4 doses was compared with extra amniotic ethacridine lactate for second trimester MTP. The mean induction to abortion interval was shorter in misoprostol group (15.5 hrs) and rate of successful abortion within 48 hrs was 95 %.

Women who did not abort within 48 hrs (10%) required further interventions. They needed PGE_2 vaginal suppositories or $PGF_{2\alpha}$ injection or D &E or oxytocin infusion.

Routine antibiotic prophylaxis may prevent upto half of all post termination of pregnancy infections and is highly cost effective.Second trimester abortion is not associated with increased complications when compared to first trimester termination of pregnancy in 5 year experience. There was no increase in complications when misoprostol was used in a woman with previous cessarian section when compared with an unscarred uteri. C.Reinun MD 1999 reported that there are good conception rates post abortally with use of misoprostol.

MIFEPRISTONE AND MISOPROSTOL COMBINATION

Only a few countries use the medical abortion regimen of mifepristone followed by a prostaglandin analogue after 2 days. Research attempts have been hampered due to limited access to the drug. Mifepristone-prostaglandin combination regimen has developed since approval and the medical method has now become more effective and better tolerated than ten years ago. In the present day regimen the dose of mifepristone is reduced to 200mg which is one third of its original dose without compromising its efficacy. Misoprostol is the most commonly used PG analogue in the regimen and this has made medical abortion safer and more cost effective. In women beyond 49 days LMP vaginally administered misoprostol has a better efficacy when compared to orally administered drug though many women prefer oral administration. This combination regimen has proven to be more acceptable to women and safe when administered under proper conditions.

Mifepristone undergoes rapid absorption after oral administration and has a half life of 30 hrs. It binds to the existing small amount of alpha acid glycoprotein and thus is quickly saturated. So oral administration of 100-800 mg mifepristone has similar peak serum levels.

Heikinheimo et al evaluated the dose response of mifepristone.The drug followed a non linear pharmacokinetics in both pregnant and non pregnant women. When a single dose of more than 100mg is administerd orally it produced only a slightly different serum peak concentrations.These pharmacokinetics data proved that smaller doses of mifepristone can be administered than the registered dose of 600mg with comparable efficacy.

World Health Organisation demonstrated repeated small doses (5 doses of 25 mg given at 12 hour intervals) or a single dose of 200 mg followed by a suitable prostaglandin is equally efficacious as a 600mg single dose. This is implemented in China where repeated small doses is used. WHO findings have been confirmed by other researchers.

NITRIC OXIDE:

Cervical ripening is defined as an increase in softening, distensibility and effacement of cervix occuring physiologically prior to onset of labour.Studies in rats have suggested that cervical ripening is associated with an increase in NO production.

Nitric oxide (NO) is an inflammatory mediator formed by the action of Nitric oxide Synthase (NOS). It has been associated with a lot of physiological and pathological processes in the female reproductive system. ***Chwalisz et al.,***

(1997) demonstrated the role of Nitric Oxide Donors in inducing Cervical ripening in guinea pigs. ***Thomson et al., (1997)*** demonstrated that NO donors caused cervical ripening in human cervix.

NO donors produced similar effects on cervical histology as that of cervical ripening at term with an inflammatory infiltrate and disruption of organisation of collagen fibrils.No effect on cervical dilatation was found in the study by Chwalisz et al ., (1997).

But ***Jane E Norman , Andrew J. Thomson , Ian A Greer (1997)*** have found that Iso sorbide Mononitrate (40 mg) applied in a single vaginal dose lowered the cumulative time for abortion compared to control group.

Hence these studies clearly indicate that NO donors can induce cervical ripening in either early or mid pregnancy when applied locally to human cervix without much of side effects. Also the use of NO donors is associated with lower incidence of abdominal pain and bleeding PV.

In inflammation iNOS can be induced by cytokines (IL-1, IL-2, IL-12), TNF-α, interferon gamma (IF-γ) and endotoxins, where NO is synthesized with a delay of 6-8 hours after stimulation. Newly synthesized NO, in turn, can stimulate the formation of cytokines, such as IL-8 in mast cells in the endometrial stroma during implantation. Nitric oxide can regulate COX activity, both constitutive COX-1 and inducible COX-2 and thereby affect the production of PGs under

normal and inflammatory conditions To take benefits of the biological effects of NO clinically, one has to utilize NO donors which, when metabolized, release NO. Thus, the nitric oxide donors glyceryl trinitrate (nitroglycerine), sodium nitroprusside and isosorbide mononitrate (IMN) are used for treatment of angina pectoris, acute myocardial infarction and congestive heart failure.

In the pregnant uterus NO donors have been used as uterine relaxants. Nitric oxide donors also promote cervical smooth muscle relaxation in early pregnancy as well as at term and have been applied clinically as cervical ripening agents.

Isosorbide mononitrate is manufactured for oral administration as a vasoactive agent, causing vasodilatation. ISMN is a potent drug, being rapidly absorbed and almost 100% bio available, as there is no significant first pass metabolism. Peak levels in plasma occur within one hour and the half-life is 5 hours. Isosorbide mononitrate is excreted via the urine.

In gynecological practice ISMN is preferentially administered per vaginum, when peak serum levels are half of the levels after oral administration but remain constant at least for six hours. It is suggested that ISMN given per vaginum, by a first uterine pass effect leads to higher concentrations in the uterus than in the serum thereby maximizing the desired effect.

A study conducted in Portugal by ***Nuneset al.,*** who reported that the association of the NO donor GTN (500 mg/kg) with dinoprostone (2 mg) in 99 women was more effective than dinoprostone alone in 97 women for cervical ripening and labour induction at term. A limitation of their study was that they did not evaluate the cervical-ripening effect of GTN alone. This beneficial effect of combination therapy (an NO donor and a PG analogue) is not unexpected and has biologic plausibility because the mechanism of action of NO donors and PGs is different and their combined use may be synergistic and lead to more effective cervical ripening.

A study conducted by ***Abdullah MS et al*** proved that a combination regimen of isosorbidemononitrate and misoprostol is more efficacious than misoprostol alone in n causing quicker cervical ripening and shortening of induction labour interval.

Nicoll AE et al conducted a study to determine the effects of vaginally administered isosorbide mononitrate (a nitric oxide donor) on maternal and fetal hemodynamics in pregnant women. They proved that vaginal administration of 20-40mg of ISMN does not produce any clinically significant hemodynamic effects on the fetus and mother .

ISMN when given to an outpatient resulted in shorter duration between admission and delivery, and required less prostaglandin use and was associated with lower incidence of uterine tachysystole .

A study conducted in ***Finland University of Helsinki*** showed that NO; a free Radical gas with a short half life is a fundamental mediator of cervical ripening. As the ideal cervical-ripening agent is one that induces cervical remodeling without stimulating uterine activity, NO donors may be such agent as they relax the myometrium while inducing cervical ripening.

Eppel et al showed in a randomized controlled study that combination of ISMN and gemeprost resulted in a shorter induction abortion interval when compared to gemeprost alone. Studies demonstrated that the NO donors, GTN and IMN, were effective cervical-ripening agents in pregnancy at term..

The ideal agent for cervical softening should be clinically effective, it should have a low side effect profile and it should be easy to administer. We hypothesize that the cervical ripening effects of nitric oxide donors and of prostaglandin might be additive.So if a small dose of nitric oxide donor is given in combination with a small dose of prostaglandin it will cause effective cervical ripening. Such combination might reduce the side effects associated with larger doses of either agent used alone. Combination therapy of prostaglandins with nitrates might therefore be an ideal method for second trimester termination of pregnancy.

AIM OF THE STUDY

AIM OF THE STUDY

1. Our aim is to compare the traditional use of vaginal misoprostol versus misoprostol and Isosorbide mononitrate in medical management of second trimester abortions.

2. The comparison involves aspects of efficacy which are evaluated by means of the difference in success rate of inducing abortion, induction to expulsion period, rate of manual/ surgical removal of the placenta and the rate of post abortive haemorrhage.

3. The comparison also includes the safety profile according to the differences in the incidence of side effects in both groups of the study e.g., fever, headache, chills, nausea and vomiting.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted in the labour ward of ***INSTITUTE OF OBSTETRICS AND GYNAECOLOGY, EGMORE (IOG)*** in the period from October 2014- July 2015. The patients included in the study were those with pregnancies from 12 to 20 weeks of gestational age undergoing induced abortion. The assessment of gestational age was based on Last Menstrual Period (LMP) and ultrasound measurement.

Following appropriate counselling and after taking informed consent by explaining about the procedure, associated complications and need for surgical evacuation as and when necessary. Required lab tests were done. Women were greater than 16 years old, healthy , 12 weeks to 20 weeks of gestational age confirmed by sonogram , and desiring an abortion.

The inclusion criteria were :

1. Patients requiring termination of pregnancy (in accordance with MTP Act) from 12 weeks to 20 weeks of gestational age.
2. Women greater than 16 years of age.

3. USG confirmation of

- Gestational Age
- Anomalies

4. Willingness to comply with visit schedule.

5. Willingness to have a surgical abortion if indicated.

Indications for Termination:

1. Anomalous baby
2. Intra uterine foetal demise (IUFD)
3. Termination for Social and Medical causes
4. Contraception failure
5. Severe Oligohydramnios
6. Severe preeclampsia or imminent eclampsia
7. PPROM

Exclusion criteria were:

1. Pregnancy below 12 weeks and above 20 weeks.

2. Previous uterine scar.

3. Hemorrhagic Disorders.

4. Long Term Anticoagulant and Corticosteroid therapy.

5. Known allergy to Mifepristone and Misoprostol.

6. Cardiovascular disorders – Angina, valvular heart disease, arrhythmia or cardiac failure

7. Contraindications to mifepristone including chronic systemic corticosteroid use or adrenal disease.

8. Contraindications to misoprostol , including Glaucoma, Mitral stenosis, sickle cell anaemia, poorly controlled seizures.

Methodology:

Study population consists of 100 pregnant women within gestational age of 12- 20 weeks.

Women were divided into two groups:

Group 1 – Combination of 400 mcg of misoprostol and 40 mg of ISMN placed intravaginally . Repeat doses included combination of 400 mcg of misoprostol and 20 mg ISMN every 4 hours for maximum 4 doses..

Group 2 - 400 mcg of misoprostol placed intravaginally every 4 hours for maximum 4 doses.

In both the above mentioned groups , T. Mifepristone 600 mg was given orally 36-48 hrs prior to termination.

On Day 1:

- Menstrual history and LMP
- Past reproductive history

- Prior pelvic surgery and known uterine anomalies
- Medical history and gynaecological examination.
- Proper pre abortion counselling in the obstetric department.
- Informed consent
- Based on Obstetric sonogram to confirm gestational age, placental location and to confirm anomalies
- ***Investigations*** – Haemoglobin and Blood group and Rh typing – If negative Anti D is given
- Screening for common sexually transmitted disease – HIV, VDRL
- Inj. T.T band prophylactic antibiotics were given to all patients.

Women received mifepristone 600 mg orally and the time of Mifepristone administration was noted. Unless abortion occurred following administration of mifepristone alone, women were asked to return 36 hours later.

(Mifepristone enters breast milk and can have endocrine effects on the baby and it has half life of 24-48 hours. Hence lactating women are advised to avoid breast feeding for 2 days).

On Day 3 –

Patient admitted in the labour room and treated as in patient.

- Preparation of parts done.
- Vitals checked.
- Per abdomen and per vaginum examination done.

- Combination of T.Misoprostol with ISMN or T. Misoprostol alone placed in the posterior fornix according to the study group.
- Reassessment done every 4 th hourly
- Vitals monitored hourly
- Analgesics, antipyretics,(Temp >100F) and anti emetics were added if required.
- Side effects like abdominal pain, fever, nausea; vomiting, diarrhoea, headache, palpitation, hypotension and tachycardia were noted.

OUTCOMES MEASURED

- Induction – Abortion Interval
- Total number of dose
- Completness of Procedure
- Failure of abortions
- Onset of side effects.

INDUCTION ABORTION INTERVAL:

Interval measured from first dose of Misoprostol to complete expulsion.

INCOMPLETE ABORTION:

If the placenta is not delivered within 2 hours, oxytocin 10 units are added in 500 ml RL at rate of 20-30 drops/min. Partial expulsion of products of conception who need an additional procedure to complete the evacuation is termed as incomplete abortion.

FAILURE:

If the women fails to abort within 48 hrs from first dose of combination of misoprostol and ISMN or misoprostol alone , it is called as failed procedure.

For each woman the outcome of the medical abortion regimen was classified into three categories.

- Complete abortion (requiring no further treatment)
- Incomplete abortion (foetus expelled but placenta not expelled even after 2 hours)
- Failures

Women with incomplete abortion were further managed by surgical intervention. Women with failures were used other methods of medical abortion.

FEVER: Fever was defined as temperature >100.4 F.

DIARRHOEA and VOMITING: were recorded as side effects if more than two episodes occurred.

BLOOD LOSS: Estimated blood loss of more than 250 ml or the need for blood transfusion was considered for significant vaginal bleeding.

Subjective assessment of the women's comfort in the two groups was also made. The women were discharged 24 hrs after the abortion if there was no complication and called for a follow-up visit after 1- 3 weeks. USG was done for all patients before discharge. Post abortion contraception counselling was also given.

In presenting the results, continuous variables are presented as means with standard deviation and ranges . Difference in continuous variables was analysed by student's T-Test for normally distributed data and Mann- Whitney U – test for skewed data. The Chi – Squared test or Fischer's exact test was used to compare categorical data when appropriate P- value < 0.05 was considered statistically significant.

OBSERVATIONS

&

RESULTS

OBSERVATION AND RESULTS

One hundred cases of second trimester abortions were included in this study and were assigned to two groups of 50 each randomly.

Group A:

Number of patients: 50

Combination of Misoprostol and Isosordibe Mononitrate was used for induction of abortion.

Group B:

Number of patients: 50

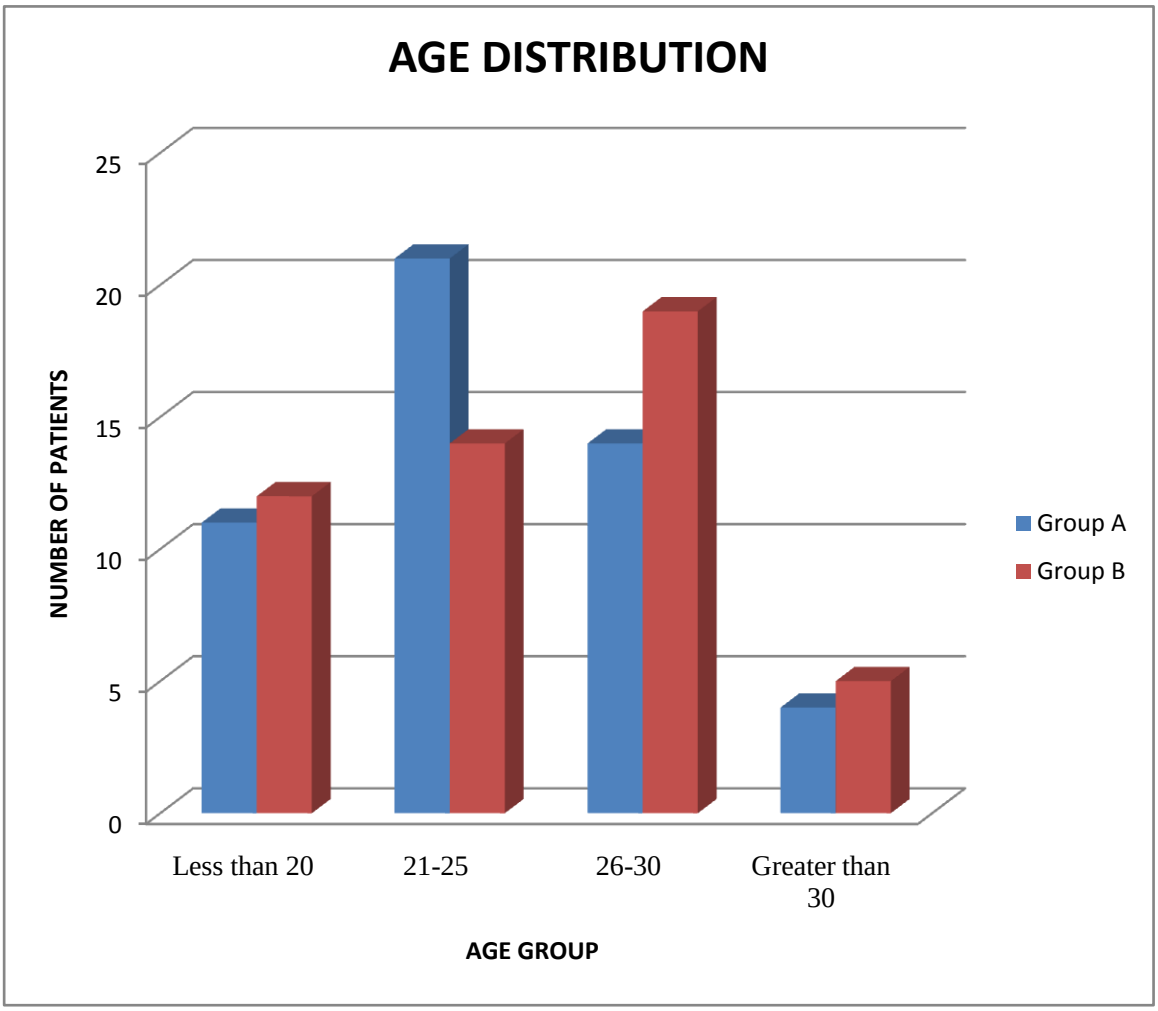
Misoprostol alone was used for induction of abortion.

The following observations were made and the results interpreted.

AGE DISTRIBUTION

Age of the patients in this study was between 18 and 36 years in both the group. The mean age was 24.42 years (Standard Deviation – 4.05) in Group A and 25.20 years (Standard Deviation – 4.37) in Group B. The maximum number of patients seeking mid-trimester abortion is in the age group 21 -25 years.

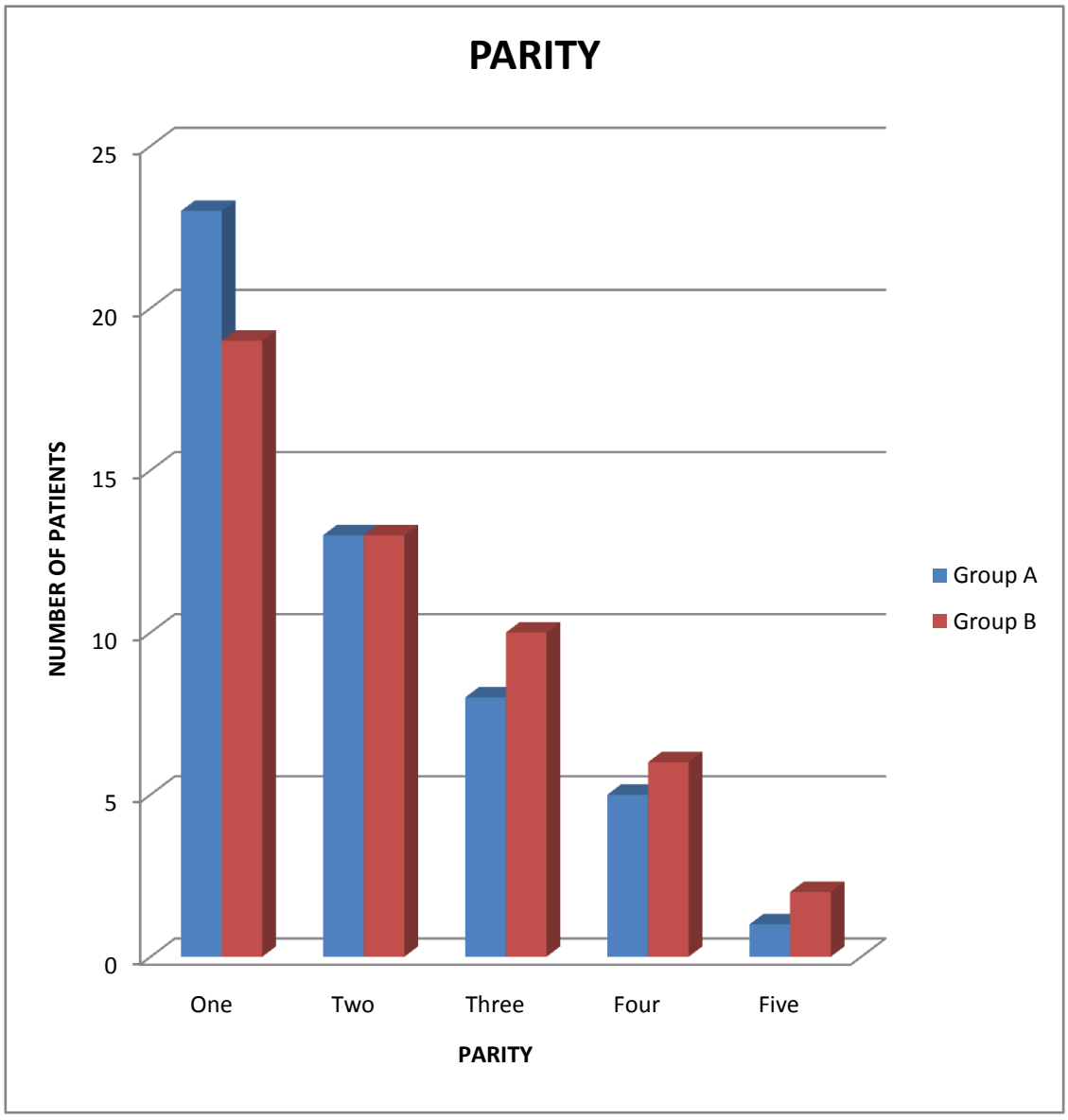
AGE GROUP (Years)	**GROUP**		**TOTAL**
	A	**B**	
Less than 20	11	12	23
21-25	21	14	35
26 -30	14	19	33
More than 30	4	5	9


AGE DISTRIBUTION
NUMBER OF PATIENTS
25
20
15
10
5
0
Less than 20
21-25
26-30
Greater than 30
AGE GROUP
Group A
Group B

PARITY DISTRIBUTION

Among all the patients studied, in Group A 46% of the patients were primigravida and in Group B 38% of the patients were primigravida. In Group A 54% of the patients were multigravida and in Group B 62 % of the patients were multigravida. Most of the patients seeking abortion in both the group were multigravida. Among multigravid women most of the patients were second gravida.

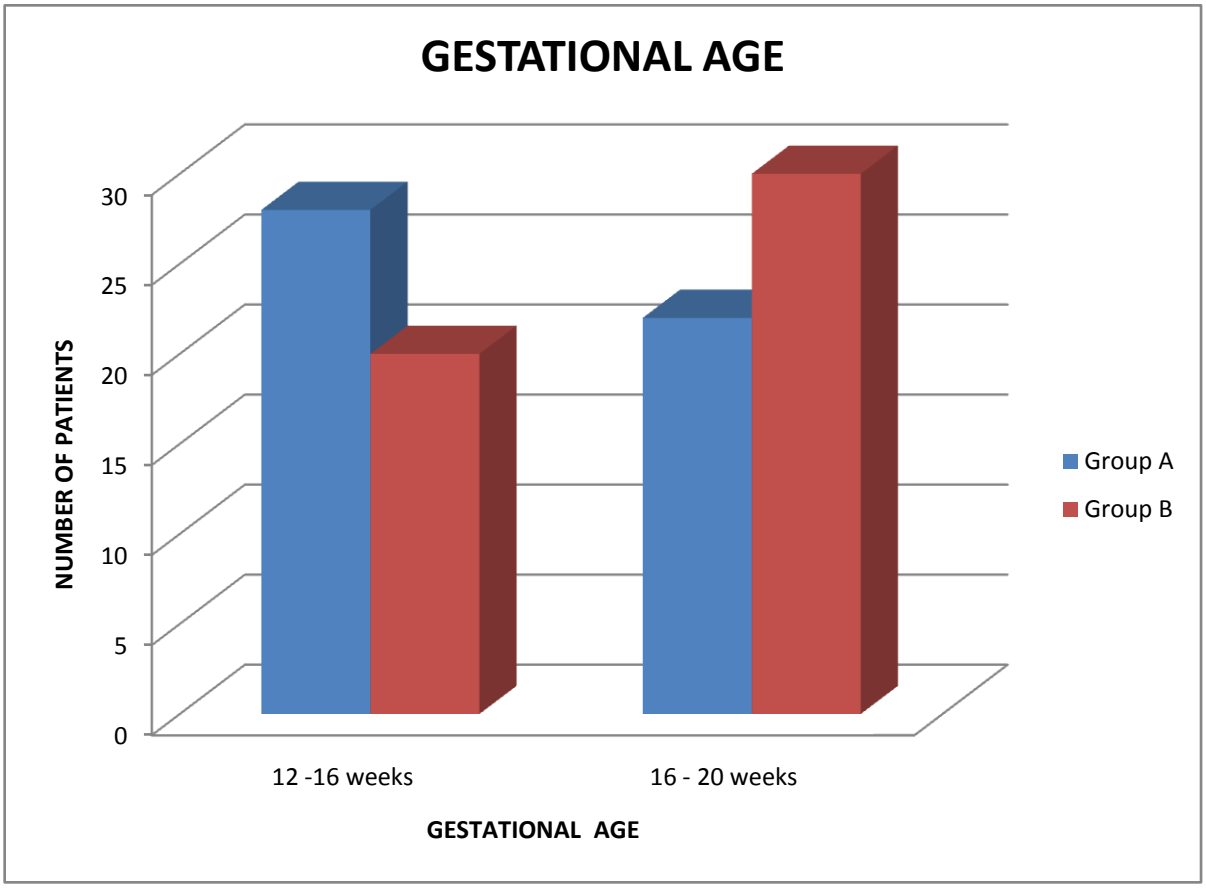
PARITY	**GROUP**		**Total**
	A	**B**	
One	23	19	42
Two	13	13	26
Three	8	10	18
Four	5	6	11
Five	1	2	3


PARITY
25
20
15
10
5
0
NUMBER OF PATIENTS
One
Two
Three
Four
Five
PARITY
Group A
Group B

GESTATIONAL AGE

Among the patients studied the gestational age were between 12 and 20 weeks. The mean gestational age was 16.24 weeks (Standard Deviation 2.26) and 16.5 weeks (Standard Deviation 2.42) in Group A and in Group B respectively.

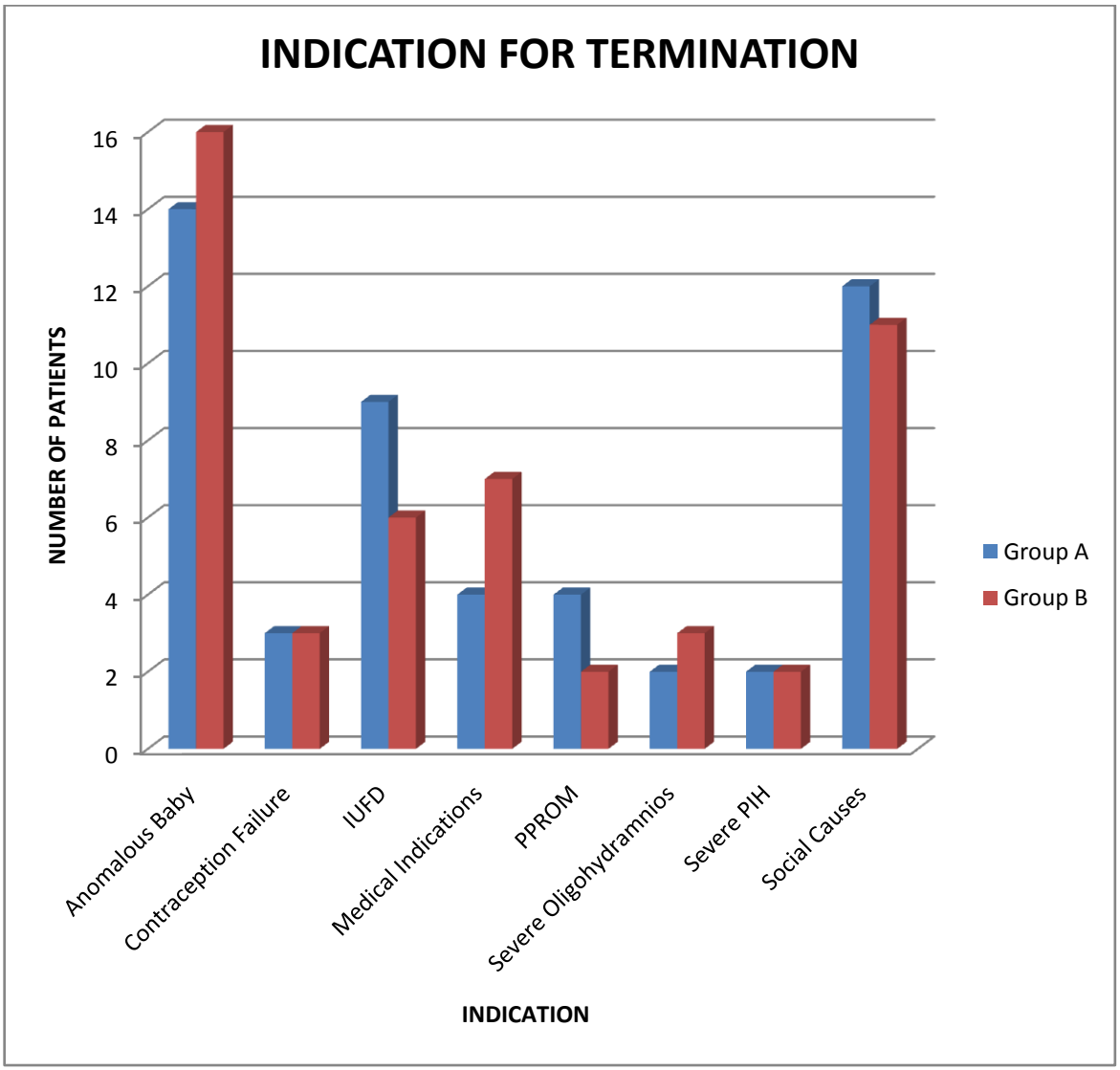
GESTATIONAL AGE	GROUP		TOTAL
	A	B	
12 – 16 weeks	28	20	48
16 – 20 weeks	22	30	52



INDICATION FOR TERMINATION

The indication for termination in majority of the patients belonging to both the group was anomalous baby. Severe PIH and Severe Oligohydramnios were the indication in few cases in both the group.

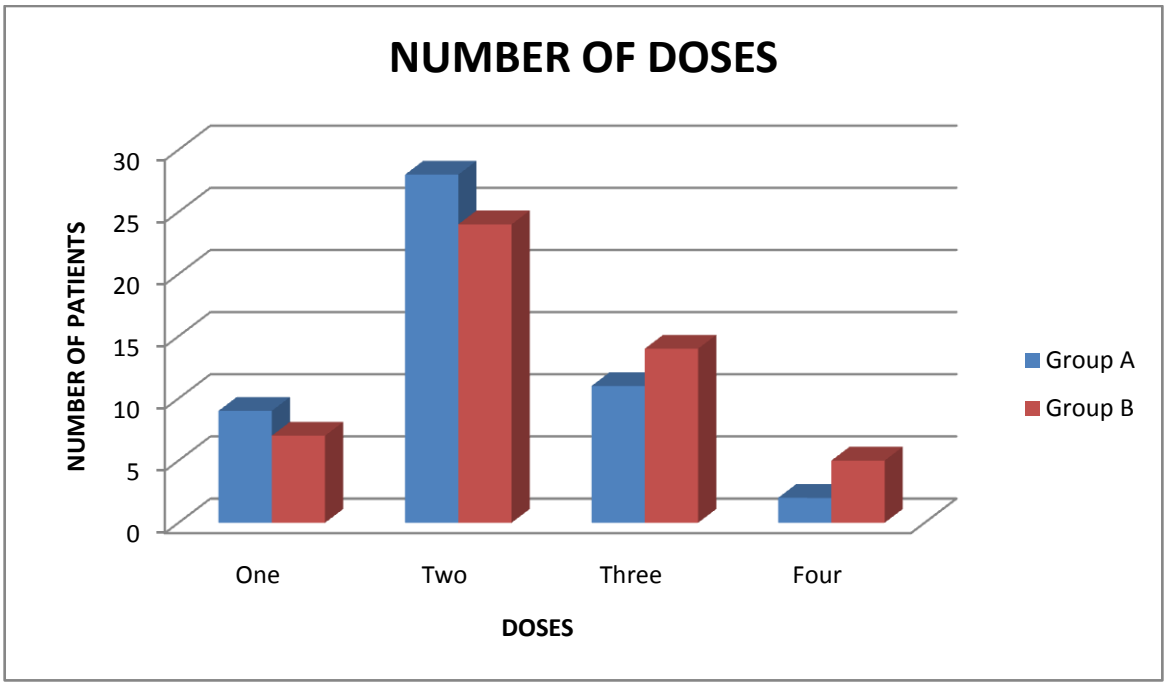
INDICATIONS	GROUP		Total
	A	B	
Anomalous Baby	14	16	30
Contraception Failure	3	3	6
Intra Uterine Foetal Demise (IUFD)	9	6	15
Medical Indications	4	7	11
Preterm Premature Rupture Of Membrane (PPROM)	4	2	6
Severe Oligohydramnios	2	3	5
Severe PIH	2	2	4
Social Causes	12	11	23


INDICATION FOR TERMINATION
NUMBER OF PATIENTS
16
14
12
10
8
6
4
2
0
Anomalous Baby
Contraception Failure
IUFD
Medical Indications
PPROM
Severe Oligohydramnios
Severe PIH
Social Causes
INDICATION
Group A
Group B

NUMBER OF DOSES REQUIRED

In Group A 18% of the patients aborted with one dose whereas in Group B 14% of the patients aborted with one dose. 56% in Group A and 48% in Group B aborted with two doses. In Group A 76% of the patients aborted with two doses where as in Group B 62 % of the patients aborted with two doses.

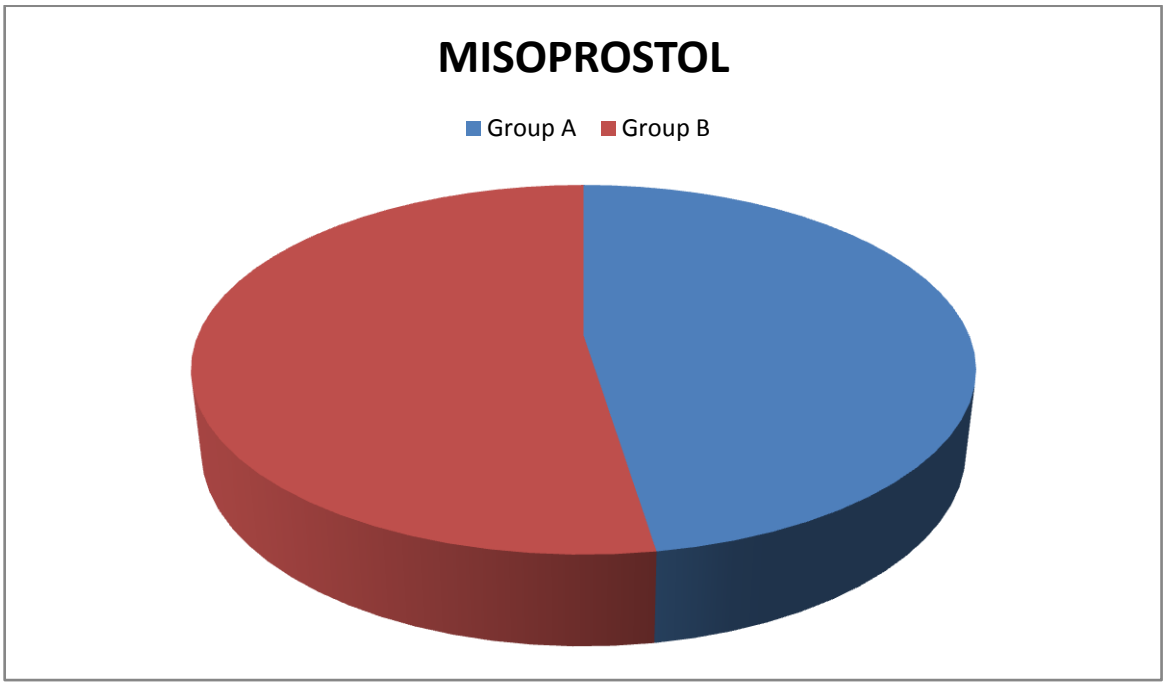
NUMBER OF DOSES	GROUP		TOTAL
	A	B	
One	9	7	16
Two	28	24	52
Three	11	14	25
Four	2	5	7



DOSE OF MISOPROSTOL REQUIRED

The mean dose of Misoprostol used in Group A was less when compared to the mean dose used in group B, but the dose reduction was not statistically significant.

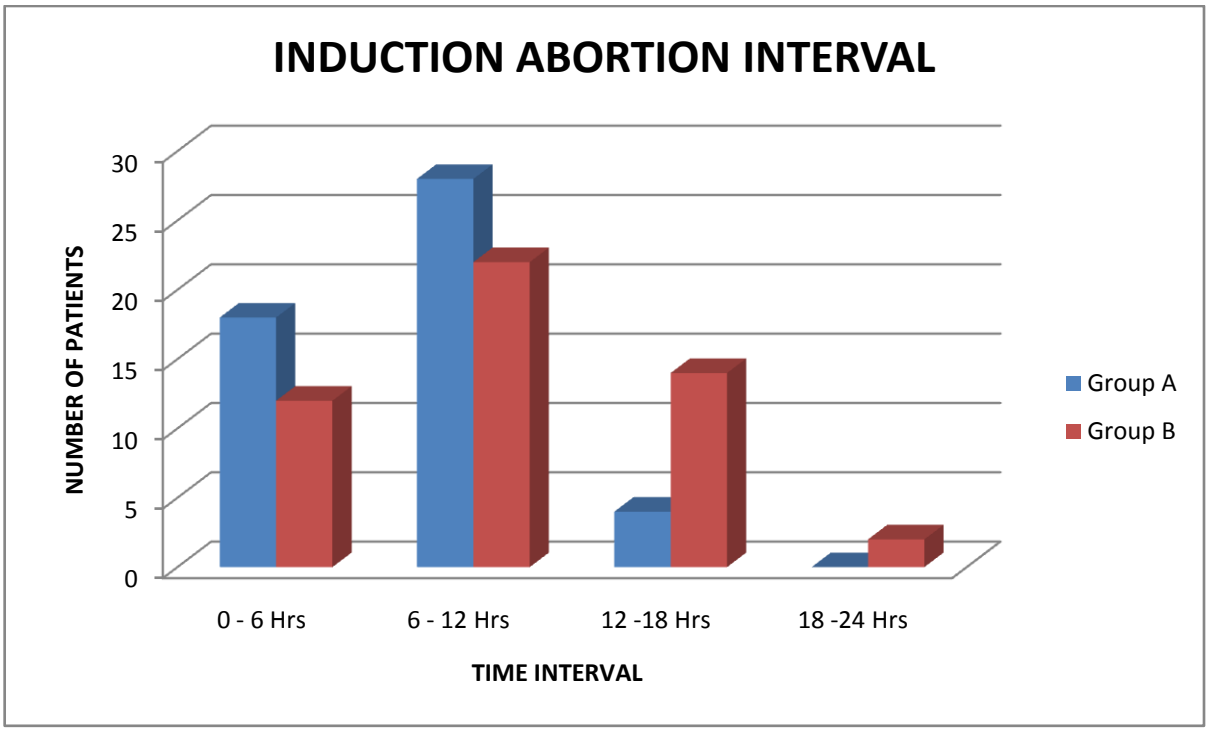
GROUP	MEAN DOSE OF MISOPROSTOL USED (µg)	P – Value
A	848	0.097
B	936	



INDUCTION ABORTION INTERVAL

In Group A the mean duration between induction and abortion was 7 hrs 36 minutes (Standard Deviation 3 hrs 11 min). In Group B the mean duration between induction and abortion was 9 hrs 55 minutes (Standard Deviation 4 hrs 42 min). The P-Value was **0.048** and was statistically significant.

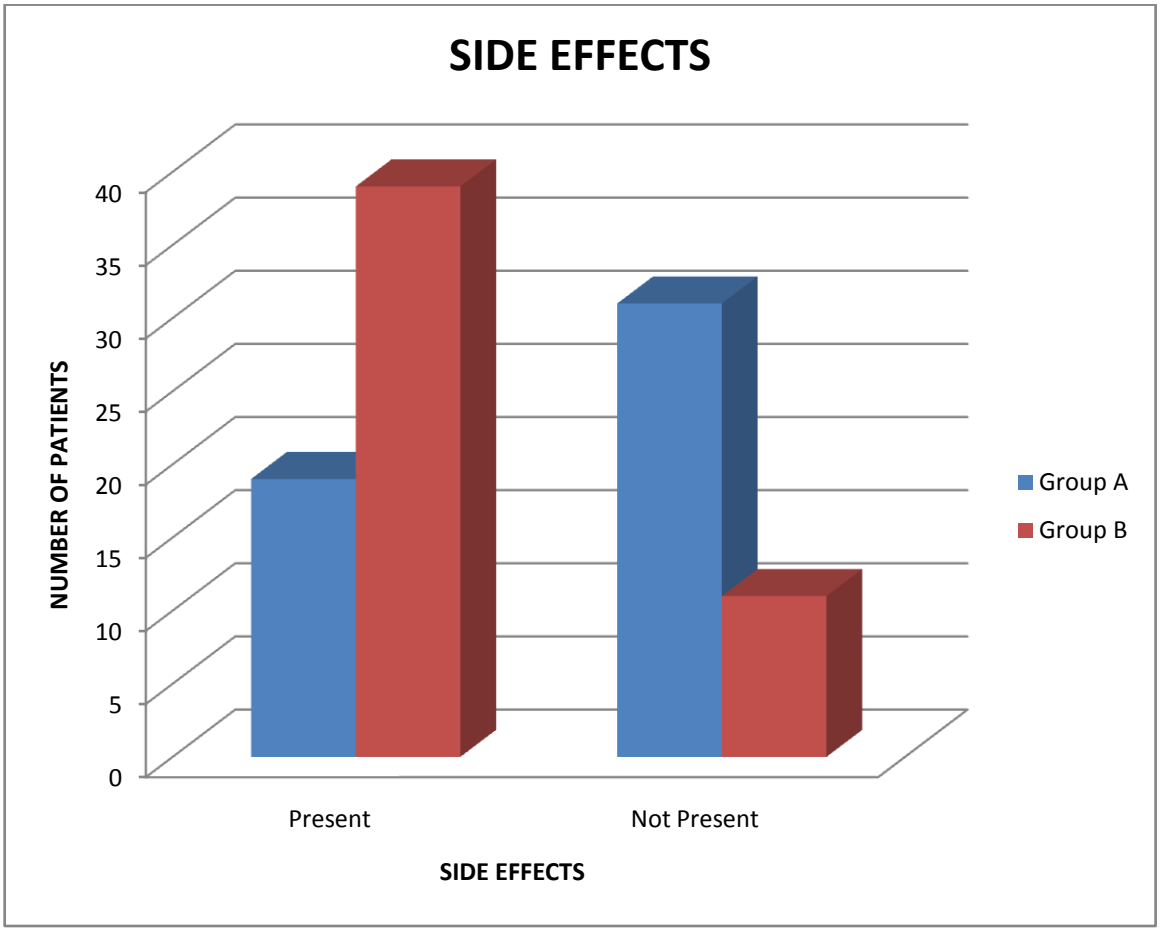
TIME INTERVAL	GROUP		TOTAL	P – VALUE
	A	B		
0 – 6 Hrs	18	12	30	0.048
6 – 12 Hrs	28	22	50	
12 – 18 Hrs	4	14	18	
18 – 24 Hrs	0	2	2	



SIDE EFFECTS

In this study the side effects of the drugs used were found in 38% and 78% of the patients in Group A and Group B respectively.

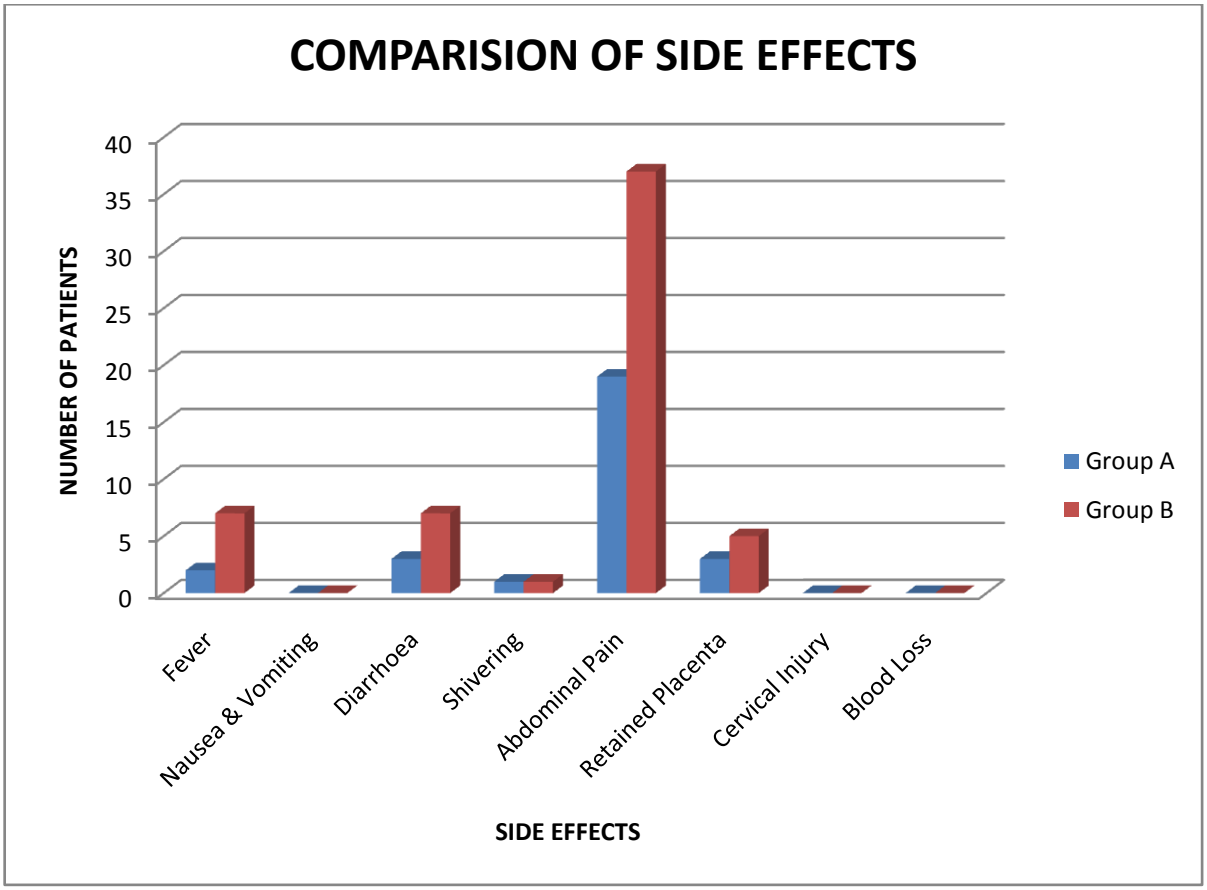
SIDE EFFECTS	GROUP A	GROUP B
Present	19	39
Absent	31	11



COMPARISION OF SIDE EFFECTS

Side effects like pain abdomen and fever were present in more number of patients in Group B when compared to Group A. Major side effects like cervical injury and blood loss were absent in both the groups. The side effect profile is reduced in Group A when compared to Group B but they are not statistically significant.

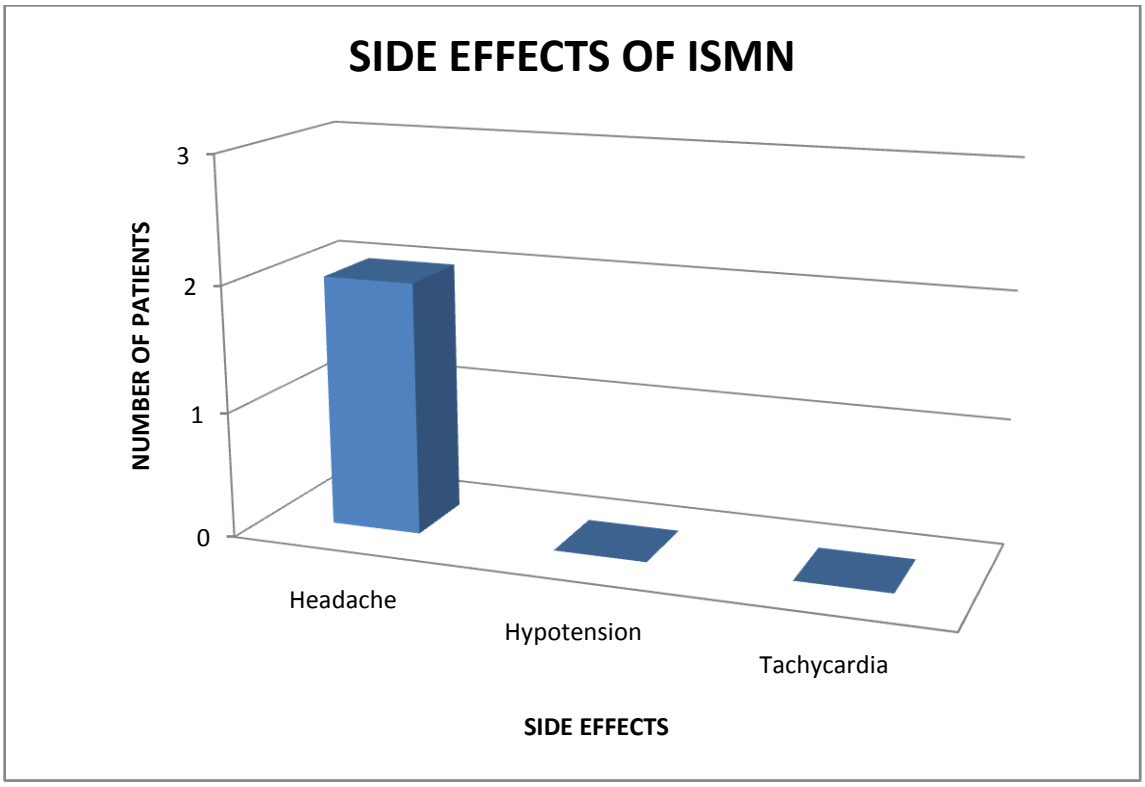
SIDE EFFECTS	GROUP A	GROUP B	P – Value
Fever	2	7	0.318
Nausea & Vomiting	0	0	0
Diarrhoea	3	7	0.318
Shivering	1	1	1
Abdominal Pain	19	38	0
Retained Placenta	3	5	0.357
Cervical Injury	0	0	0
Blood Loss	0	0	0


COMPARISION OF SIDE EFFECTS
NUMBER OF PATIENTS
40
35
30
25
20
15
10
5
0
Fever
Nausea & Vomiting
Diarrhoea
Shivering
Abdominal Pain
Retained Placenta
Cervical Injury
Blood Loss
SIDE EFFECTS
Group A
Group B

SIDE EFFECTS SPECIFIC TO ISOSORBIDE MONONITRATE

Patients in Group A who were induced with additional drug had the following side effects in addition to the above side effects. These side effects occurred in only few of the patients.

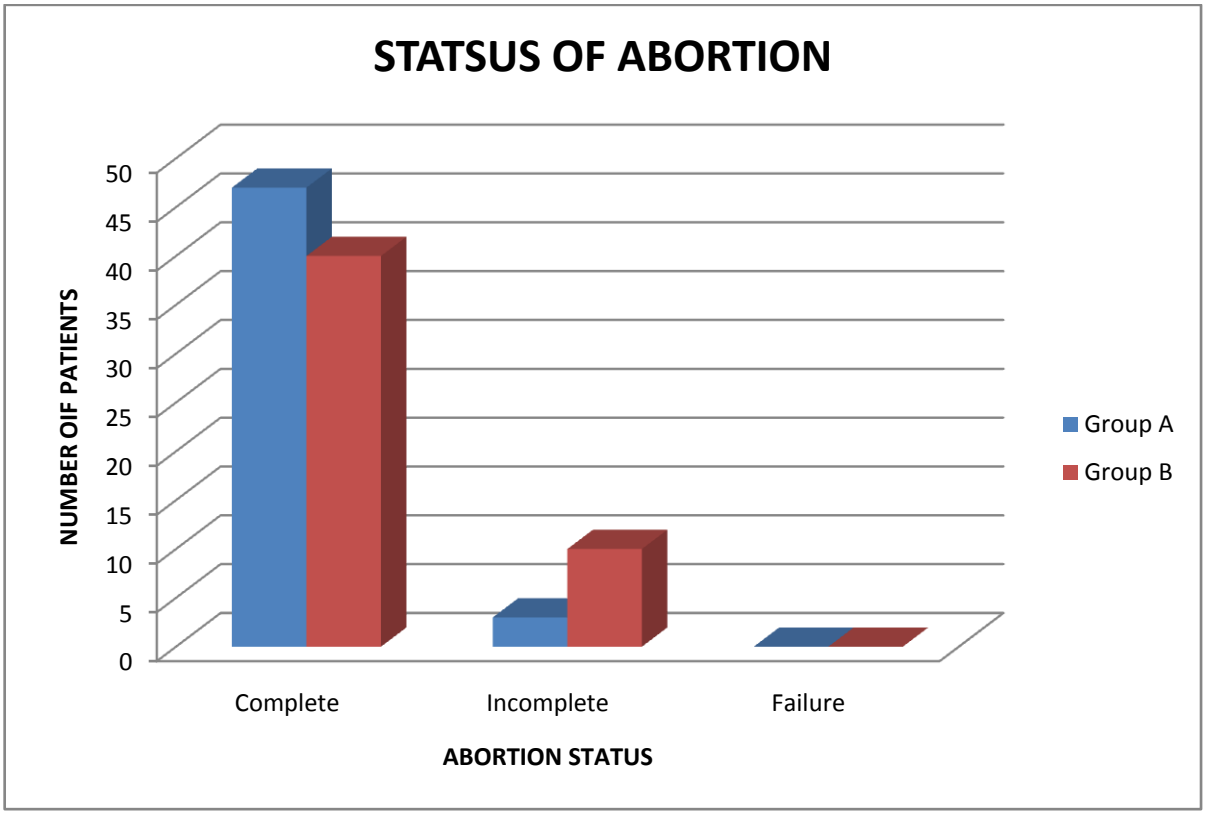
SIDE EFFECTS	NUMBER OF PATIENTS
Headache	2
Hypotension	0
Tachycardia	0



STATUS OF ABORTION

Among the patients studied 94% in Group A and 80% in Group B had complete abortion whereas 6% and 16% of women in Group A and Group B respectively had incomplete abortion. There was no failure of abortion in both the group. The number of complete abortion were more in Group A when compared to Group B but the results were statistically not significant.

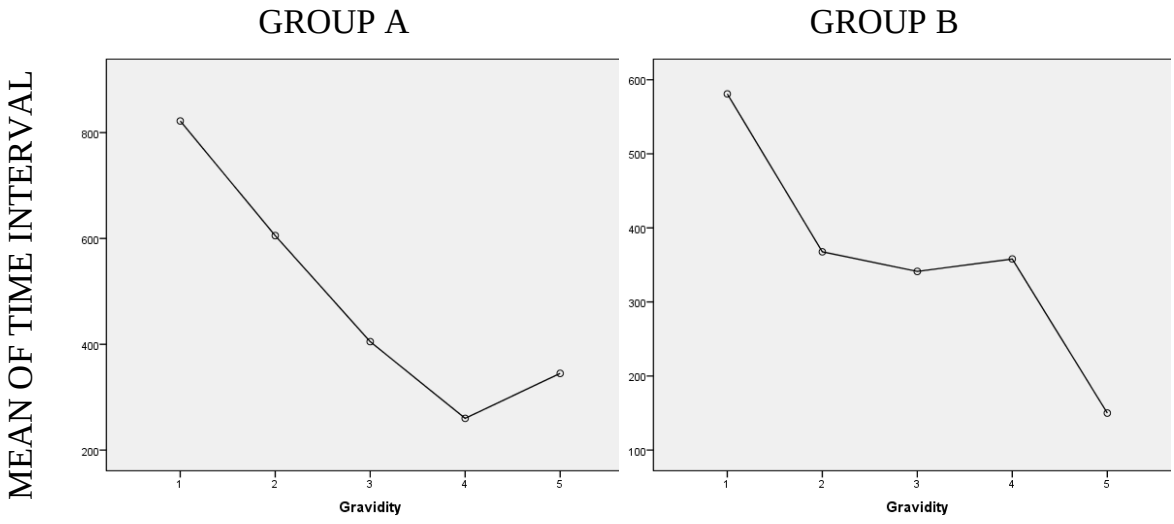
OUTCOME	GROUP A	GROUP B	P – VALUE
Complete Abortion	47	40	0.318
Incomplete Abortion	3	10	
Failure	0	0	

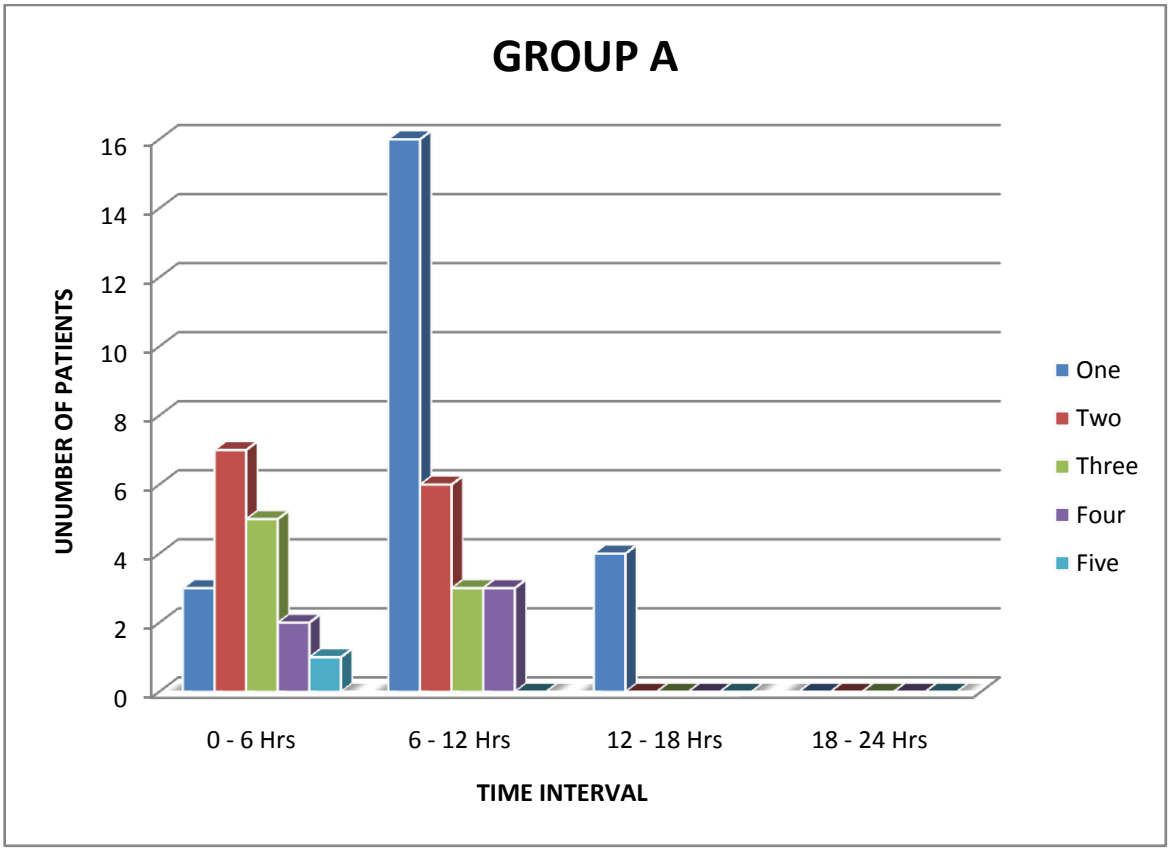


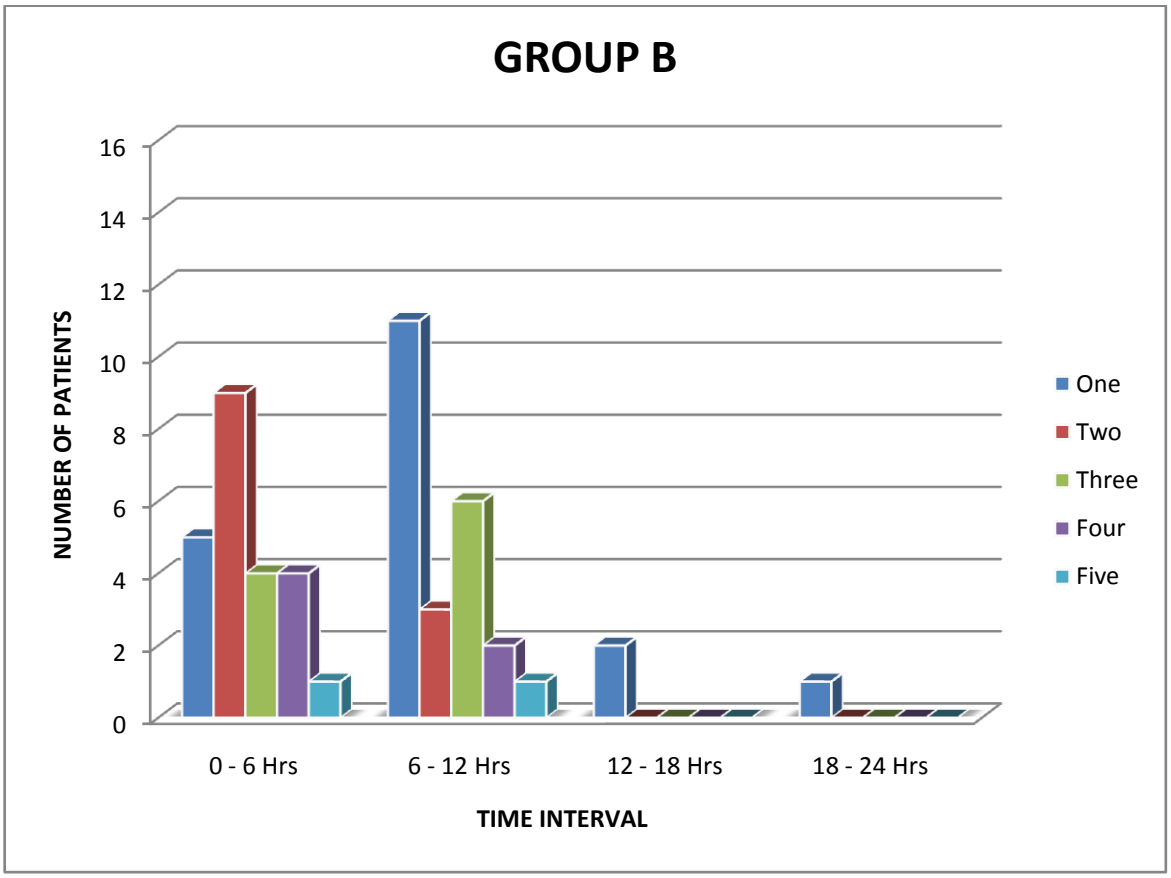
PARITY AND INDUCTION ABORTION INTERVAL

As the gravidity increases the induction abortion interval in both groups decreases. This is irrespective of the drug used.

TIME INTERVAL	PARITY			
	GROUP A		GROUP B	
	PRIMI	MULTI	PRIMI	MULTI
0 – 6 Hrs	3	15	5	18
6 – 12 Hrs	16	12	11	12
12 – 18 Hrs	4	0	2	0
18 – 24 Hrs	0	0	1	0



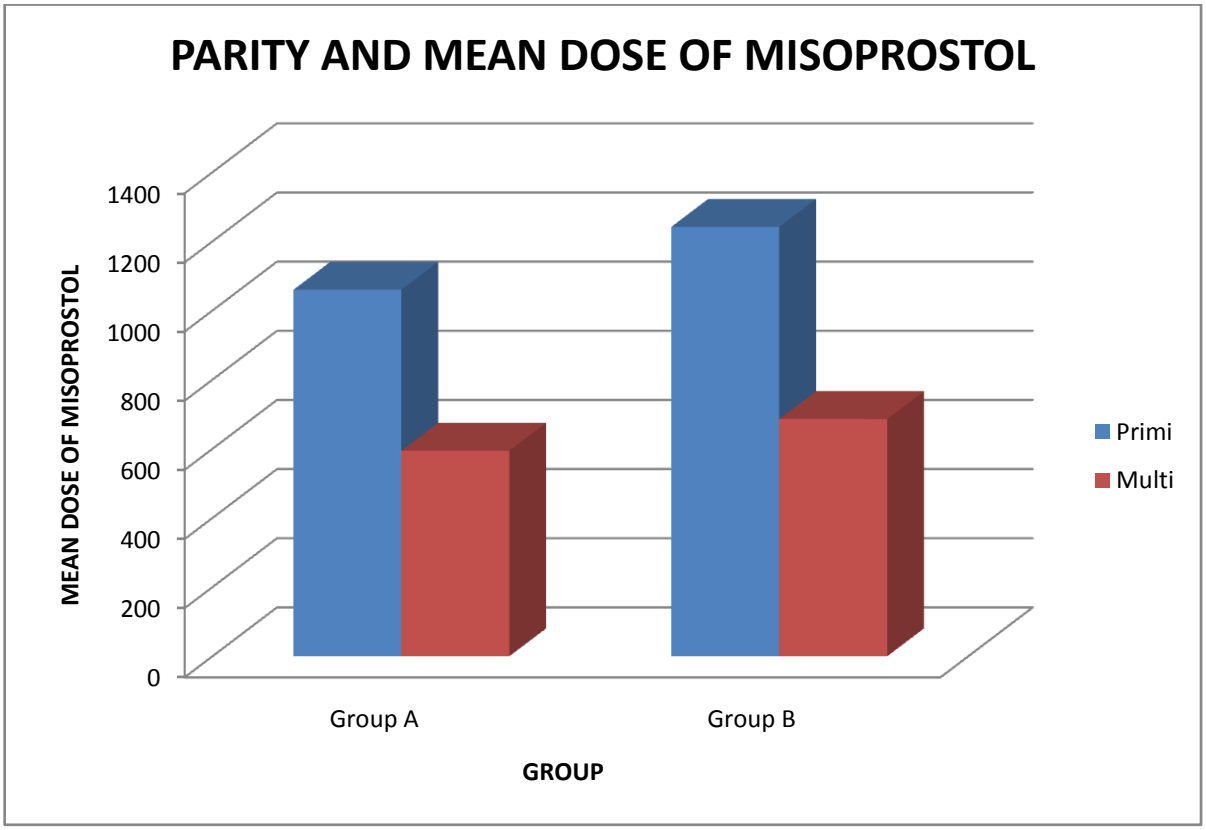

GROUP A
UNUMBER OF PATIENTS
16
14
12
10
8
6
4
2
0
0 - 6 Hrs
6 - 12 Hrs
12 - 18 Hrs
18 - 24 Hrs
TIME INTERVAL
One
Two
Three
Four
Five


GROUP B
NUMBER OF PATIENTS
16
14
12
10
8
6
4
2
0
0 - 6 Hrs
6 - 12 Hrs
12 - 18 Hrs
18 - 24 Hrs
TIME INTERVAL
One
Two
Three
Four
Five

PARITY AND MEAN DOSE OF MISOPROSTOL

As the parity increases the mean dose of misoprostol used reduces irrespective of the study group.

MEAN DOSE OF MISOPROSTOL	PARITY	
	PRIMI	MULTI
GROUP A	1060	594.5
GROUP B	1242	686.25



DISCUSSION

DISCUSSION

The exact incidence of induced abortion is definitely not known, as estimated amount of illegal abortions are not documented reliably. In 2007, it was estimated that 42 million abortions occurred each year in the world out of which 26 million were legal and 20 million were illegal.

The human uterine cervix is a unique organ. It is composed of smooth muscle cells (10-15%) and connective tissue (85-90%). During the time of pregnancy the cervical stroma mainly consists of extracellular connective tissue, type I and III collagen bundles which provide rigidity and competence to the cervix. The contents of matrix include water, glycosaminoglycans, and proteoglycans as well as dermatan sulfate, hyaluronic acid, and heparin sulfate.

Cervical ripening is an active process, involving a complex cascade of degradative enzymes which is accompanied by degradation and disorganization of collagen framework, an increased water content, and rearrangement of extracellular matrix proteins and glycoproteins. It resembles an inflammatory reaction.

Prostaglandins are regarded to play a crucial role among the factors that regulate cervical ripening. The other factors include: mechanical factors, estrogens, cytokines, neuropeptides , and other inflammatory agents

Nitric oxide is a free radical gas, whose half-life is short - 4 s. It is considered as a fundamental mediator of cervical ripening. ***An ideal cervical-ripening agent is one that induces cervical remodelling without stimulating uterine activity***. Nitric oxide donors are one such agent which relaxes the myometrium and at the same time induces ripening of cervix.

The current study demonstrates that the combination of ISMN and misoprostol is more effective for second trimester termination of pregnancy than either ISMN or misoprostol alone and results in a ***shorter INDUCTION TO ABORTION INTERVAL,*** thus reducing the dosage of drugs used and therefore their side effects.

This is a prospective study done in 100 women with 12 to 20 weeks of pregnancy undergoing medical termination. The maternal variables such as marital status, age , parity, gestational age were noted. Subsequently the medical abortion regimen of 600 mg of Mifepristone and 400 mcg of vaginal misoprostol alone or in combination with 40 mg of ISMN was prescribed. The complete abortion rate, induction abortion interval, total dose of misoprostol used and side effects of misoprostol were noted in group A and B.

Several studies have evaluated the use of Iso sorbide mono nitrate for termination of pregnancy in second trimester as well as in term. Comparison of these studies is difficult because they included women with varying duration and different regimens.

AGE:

The mean age in this study was 24.6 +/- 4 Standard Deviation. The age distribution was maximum amongst the 20 to 25 years and least amongst more than 30 years.

PARITY:

Parity distribution shows the maximal distribution among primi gravida women -46% in group A and 38% in group B and the rest were multigravida. In this study, all patients aborted without failure

In Group A, 37.25% of primigravida and 74% of multigravida aborted within 12 hours. Multigravid women took significantly less time to abort (P-value -0.044).

In Group B, 32% of primigravida and 60 % of multigravida aborted within 12 hours. As the parity increases the mean induction abortion interval decreases in both the groups.

GESTATIONAL AGE:

Gestational age distribution was taken as 12 to 16 weeks (56% and 46%) and 16 to 20 weeks (44% and 60 %) in group A and group B respectively. The minimum gestational age in this study was 12 weeks and the maximum was 20 weeks with a mean gestational age of 16.05 weeks +/- 2 standard deviation. The mean gestational age was 16.24 weeks (Standard Deviation 2.26) and 16.5 weeks (Standard Deviation 2.42) in Group A and in Group B respectively.

Mean amount of misoprostol used in patients between 12-16 weeks of gestation was more or less equal compared with mean amount used in gestation between 17- 20 weeks (618 vs 664) in group B and shows no statistical significance.

INDICATIONS FOR TERMINATION:

The most common indication in the study was Anomalous baby (28 % and 32 %) in group A and B respectively. The indications like Severe PIH and Severe Oligohydramnios were less. Medical indications included Severe IUGR, uncontrolled Diabetes, Maternal medical complications like heart disease, SLE, Chronic kidney disease, Chronic liver disease. According to Susanne et al in 2010 may the most common indication were medical illness, social reasons and anomalies.

INDUCTION ABORTION INTERVAL:

In the present study the time taken for complete abortion in group A ranged from 2.5 hrs to 15 hrs. In Group A the mean duration between induction and abortion was 7 hrs 36 minutes (Standard Deviation 3 hrs 11 min). In Group B the mean duration between induction and abortion was 9 hrs 55 minutes (Standard Deviation 4 hrs 42 min). The P-Value was **0.048** and was statistically significant.

In spite of all the other factors remaining the same, the mean induction abortion interval in group A is lesser and is due to the addition of ISMN as an additive drug for termination.

MEAN DOSE OF MISOPROSTOL USED :

The mean dose of misoprostol used was lesser in Group A when compared to Group B (848 vs. 936) but however it is not statistically significant. The lesser mean dose of misoprostol used is attributed to the use of ISMN as an additive inducing agent.

MEAN NUMBER OF DOSE USED :

In Group A 76% of the patients aborted with two doses where as in Group B 62 % of the patients aborted with two doses. Though it is not statistically significant, the number of doses used for most of the patients in Group A is less when compared to Group B, where only 60 % patients aborted with two doses.

SUCCESS RATE:

The success rate of abortion was determined by complete abortion within 48 hours and in our study it was 94 % in Group A and 80 % in Group B. Also in group A almost all the patients aborted within 15 hrs whereas the time was prolonged in Group B where ISMN was not added. The complete abortion rate in Group A was statistically significant (P value 0.0005).

The abortion was considered incomplete if placenta was not expelled within 2 hrs or if there was presence of retained products of conception which requires an intervention like check curettage. The incomplete abortion rate and need for check curettage was higher in group B compared to group A (16 vs. 6 %) which is statistically significant. In both the groups there was no failure of abortion.

There are only few studies reporting regimens for women who do not abort within 24 hrs. According to some protocols, if abortion does not occur, mifepristone is given followed by repeated vaginal administration of drugs. Any patient who fails to abort during the second day will get a third dose of mifepristone followed by gemeprost 1 mg every 3 hrs.

The concept of genetic variation of the progesterone receptor has been postulated in first trimester abortion among women who did not respond to mifepristone – PG combination.

Still more studies are required to look into the prolonged or failed second trimester abortion.

SIDE EFFECTS :

Side effects like pain abdomen and fever were present in more number of patients in Group B when compared to Group A. Apart from pain abdomen and fever , the incidence of adverse effects was relatively low in both groups.

Pain abdomen was seen in 38 % in Group A and 76 % in Group B. This shows that the addition of ISMN has a definite reduction in the side effect. This is due to the antagonistic effect of ISMN on myometrial contractility without interfering with the abortion process.

Side effect specific to ISMN was negligible and reported only in 2 out of 50 patients. This is in accordance with the study which tells that vaginally ISMN has only local absorption and it enters into systemic circulation only after a maximum of 100 mg.

SAFETY OF MEDICAL ABORTION :

It is important to note that, despite advances in abortion technology , procedure related morbidity and mortality increases with gestational age. Vacuum aspiration is one of the safest surgical procedures, and the experience with medical abortion to date suggests that this method is also safe when provided at clinics with adequate back up services . Antiprogestogen ,Prostaglandins and Nitrates have contraindications that have to be respected. As a special precaution, the medical method is not recommended for use in women who are older than 35 years and who smoke more than ten cigarettes a day.

NITRATES AS A GOOD CERVICAL RIPENING AGENT :

Nitrates have an antagonistic effect in the myometrium that is stimulated by PGs and relaxed by NO donors, resulting in less frequent episodes of uterine hyperactivity. In our study, combination therapy resulted in a slight decrease in the incidence of uterine hyperactivity.

Furthermore, we hypothesized that combining ISMN with misoprostol might reduce the side effects associated with either drug alone because the smooth-muscle-relaxant properties of ISMN may result in a reduced incidence of the side effects attributable to PG-associated gastrointestinal and myometrial contractions.

In our study, we found that the addition of ISMN does reduces the incidence of abdominal/pelvic pain or the need to opiate analgesia in the first 24 hours..In contrast, combination therapy reduced significantly the incidence of headache. The current study demonstrates that vaginally administered ISMN does not affect maternal hemodynamic .This is in agreement with the findings of ***Nicolle et al*** in their randomized controlled trial of IMN in the third trimester

A potential concern regarding the use of NO donors is that their uterine-relaxant effect may promote increased blood loss at the time of delivery. However, the current study reveals that the incidence of postpartum haemorrhage

was similar in the study groups. This finding is supported by results of previous studies.

As no maternal side effects of clinical importance were registered with the NO donor ISMN in the current study, such an agent could be given for cervical ripening. Maternal enthusiasm for ISMN was clearly evident because maternal satisfaction and acceptability were found to be higher in the ISMN and misoprostol combination group compared with the misoprostol alone group.

In this study we compare two regimen, Misoprostol with ISMN and Misoprostol alone vaginally every 4 hrs following oral mifepristone (600 mg)in gestational age between 12 and 20 weeks of pregnancy (second Trimester)

The abortion rates and the mean induction abortion interval was significantly more in Group A when compared to Group B.

SUMMARY

SUMMARY

This comparative study was done in the Department of Obstetrics and Gynaecology, Institute of Obstetrics and Gynaecology, Madras Medical College.

A total of 100 patients with gestational age 12- 20 weeks pregnancy undergoing Medical Termination of Pregnancy were enrolled in this study.

OUTCOME	**GROUPA (Miso and ISMN)**	**GROUP B (Misoprostol alone)**
InductionAbortion Interval	7 hrs 36 mins	9 hrs 55 mins
Tot.amt Misoprostol used	848 mcg	936 mcg
Complete Abortion rate	94%	80%
Incomplete Abortion rate	3%	20%
Side effects present	38%	78%

- All patients after appropriate investigations and counselling were given oral Mifepristone 600 mg followed 36- 48 hrs later by vaginal misoprostol 400 mcg with ISMN 40 mg every 4^{th} hrly in one group and vaginal misoprostol alone 400 mcg every 4 th hrly in another group.
- There were no significant changes in considering age, socio economic status, marital status, parity and gestational age distribution.
- The average age was 25 years and the mean parity in this study was 2.8.
- Most common indication for MTP was anomalous baby and social reasons in this study.
- The mean induction abortion interval was significantly less (7 hrs 36 mins) in Group A, compared with group B(9 hrs 55 min).
- There was no statistical significant difference in the amount of mean dose used in both groups. But however the mean dose decreased in group A (848 mcg) when compared with group B (936 mcg).
- The mean number of doses was more or less same in both the groups.
- The complete abortion rate within 48 hrs in Group a A was 94 % which shows no statistical significance when compared with Group B complete abortion rates (80%). However, it is interpreted that on adding ISMN the number of complete abortion rates are higher.
- There was no failure of abortion in both the groups.
- The side effects such as pain abdomen and fever were less in Group A(38 %) when compared to Group B(78%).

- Side effects specific to ISMN was very less and reported only in 2 % of study groups. There were no significant changes in average Pulse Rate, average Systolic BP, and Diastolic BP in the study group before and after the administration of intravaginal ISMN.
- In both the groups, as the parity increases the mean dose of misoprostol used and induction abortion rate decreases.
- None of the patients in study group required extra dose of methergine, volume expanders, blood or blood products.
- The drug ISMN , was also economical and cost effective. One tablet of ISMN (40 mg) costs around Rs . 4 – Only. Also when ISMN is added there is a reduction in hospital stay, manpower, economy spent on patient and a sense of well being from the patient also.

CONCLUSION

CONCLUSION :

To conclude Group A (600 mg of Mifepristone on Day 1 followed by 36-48 hrs combination of intravaginal Misoprostol and ISMN every 4 th hrly) shows following results :

- 100 % abortion rate within 24 hrs
- The mean induction abortion interval was significantly less
- There was no failure of abortion.
- Mean dose of misoprostol used was lesser.
- Side effects such as pain abdomen and fever were reduced in group A
- There was no reported evidence of postpartum haemorrhage or increased blood loss.

Hence seems to be the effective regimen for second trimester medical abortion (12-20 weeks).

The ideal regimen with optimal doses and frequency of administration of combined therapy awaits further studies. Vaginally administered ISMN seems to be safe and well tolerated and provides a merit in some situations, where uterine contractions are unwanted before cervical ripening.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. The Medical Termination of Pregnancy acts 1971 (Act no. 34 of 1971)
2. Population reports series F No.3 Jan 1973, Theresa Vander Vlugt and P.T.Piotrow
3. The Medical Termination of Pregnancy rules 1975, published in the Gazette of India Pt II Sec.3(1), Oct.1975
4. Population Reports Series F No.6, Sep.1977, Emiline Royco Ott, Ph.D et al
5. The physiology of cervical ripening and cervical dilatation and the effect of
    a. abortifacient drugs, Uldbjerg N.Ulmstern U 1990.
6. Family Welfare Programme in India. Year Book 1993-94 of Family Welfare,
    a. Govt of India, New Delhi, 1994
7. Complications of Abortions : Technical and Managerial Guidelines for prevention And Treatment, Geneva WHO : Jaypee Brother 27-31, 1995
8. Global overview of abortion and future strategies to reduce death due to abortion,Chakraborty BK, Jaypee Brother : New Delhi, 1995.

9. Changes in mRNA levels of Nitric Oxide Synthases in rat uterus and cervix during Pregnancy, Ali M, Yallampalli C, Chwalisz K, Soc. Gynecology in=vest 1995, 2:80

10. Drugs used in the treatment of cardiac ischemia, Robertson RM, Robertson D,

    a. Goodman and Gilman's Pharmacological Basis of Therapeutics, 1995, 759-79

11. Pregnancy termination, Chaudhuri S.K, Practice of Fertility Control

12. Abortions – Clinical Gynaecology IV Edition, Bhasker Rao K, Roy Chowdhry N.N

13. Nirtic Oxide and the myometrium. Norman J, Pharmacol Ther 1996; 70 : 91-100

14. Cervical ripening after Nitric oxide Donors, Norman JE, Thomson AJ, Grusin – Human reproduction 1998, Vol.13, 251-252.

15. Randomised Control Trial of Nitric Oxide (vs) PG for cervical ripenig before First Trimester Termination of Pregnancy, Thomson AJ, Lunan CB, Ledingham M, Howat RC, Cameron IT, Greer IA, Norman JE, Lancet 1998, 352 (9134) : 1093-1096.

16. Therapeutic Drugs, Dollery C. Boobis A, Rawlins M, Thomas S, Edinburgh : Churchill Livingstone, 1999: G31-G34.

17. Nitric Oxide Donors stimulate PGF2 alpha and inhibit thromboxane B2 production in the human cervix during the first trimester of pregnancy, Ledingham M, Denison FC, Kelly R, Norman JE, Mol Hum Reprod 1999; 5(10) 973-982.

18. A Novel cervical dilatation force measurement instrument, Richardson W.Smith D.C. Journal of Medical Engineering and Technology, Vol.13,No.4 July/August-1999, 220-221.

19. Direct causes of maternal death, Geneva WHO 1999, Reduction of Maternal Mortality, A Joint WHO/UNFPA/UNICEF.

20. Role of intravaginal Isosorbide Mononitrate in cervical ripening prior to First Trimester MTP : Veena Agarwal, Asian Journal of Obst. And Gynec Practice, Vol.5, No.4, Sep – Nov.2001,22-24.

21. Making Motherhood Safer, Oncoming obstacle, Elizabeth I, Nancy V, Population Review Bulletin, Feb 2002

22. Jozwiak M et al.: Mechanical methods for induction of labour. The Cochrane Library, Issue 3 , 2012

23. Royal College of Obstetricians and Gynaecologists /RCOG/: The Care of Women Requesting Induced Abortion: Summary. Revised edition published November, 2011
24. Chambers DG et al.: Comparison of Dilapan-S and laminaria for cervical priming before surgical pregnancy termination at 17-22 weeks' gestation. International Journal of Women's Health 2011:3 347-352
25. Mozurkewich EL et al.: Methods of induction of labor: A systematic review. BMC Pregnancy and Childbirth, 2011, 11:84
26. Wilson LC et al.: Cervical preparation for surgical abortion between 12 and 18 weeks of gestation using vaginal misoprostol and Dilapan-S. Contraception. 2011 Jun;83(6):511-6. Epub 2010 Dec 3
27. Roztočil A: Labor Preinduction and Induction – Recommended Steps – Revised, 2010
28. Kapp N et al.: Cervical preparation for first trimester surgical abortion. The Cochrane Library, 2010 www.thecochranelibrary.com
29. Newmann SJ et al.: Cervical preparation for second trimester dilation and evacuation. The Cochrane Library, 2010 www.thecochranelibrary.com
30. Drey EA et al.: How Research Guides Clinical Practice: Cervical preparation for surgical abortion from 20 to 24 weeks' gestation. Reproductive Health, 2010
31. Binder T.: Is Our Approach to Post Term Pregnancy Correct? Actual Gyn 2009, 1, 30-33,www.actualgyn.com

32. Samuel MI et al.: Hygroscopic dilator (Dilapan-S) and misoprostol combination for the early first-trimester termination of pregnancy. J Fam Plann Reprod Health Care. 2009 Jan;35(1):45-7
33. Hayes JL et al.: Cervical dilation in second-trimester abortion. Clin Obstet Gynecol. 2009 Jun;52(2):171-8
34. Newmann S et al.: Cervical preparation for surgical abortion from 20 to 24 weeks' gestation. Contraception , Contraception 77 (2008) 308-314
35. Heinemann J et al.: Do mechanical methods of cervical ripening increase infectious morbidity? American Journal of Obstetrics & Gynecology, August 2008, 177-188
36. Carbonell Esteve JL: SURGICAL METHODS in 2nd TRIMESTER ABORTION. Reproductive Health and Responsibilities, 24/25 October 2008 - Berlin, Germany
37. Tan EL et al.: Are Hygroscopic Dilators Better than Vaginal Prostaglandins for Induction of Labour? SGH PROCEEDINGS, VOL 17, NO 3,2008
38. Jansen NJ et al.: Mifepristone and misoprostol versus Dilapan and sulprostone for second trimester termination of pregnancy. The Journal of Maternal-Fetal and Neonatal Medicine, 2008 21(11): 847-851
39. Carbonell Esteve JL et al.: Late second-trimester abortions induced with mifepristone, misoprostol and oxytocin. Contraception. 2008 Jul;78(1):52-60. Epub 2008 May 21

40. Chen, FC et al.: Isosorbide mononitrate vaginal gel versus misoprostol vaginal gel versus Dilapan-S for cervical ripening before first trimester curettage. Eur J Obstet Gynecol Reprod Biol. 2008 Jun;138(2):176-9. Epub 2007 Nov 5
41. Fox MC et al.: Cervical preparation for second-trimester surgical abortion prior to 20 weeks of gestation. Contraception 76 (2007) 486-495

ANNEXURES

PROFORMA

Name :

Age :

IP. No. :

LMP :

EDD :

GA :

Parity :

SE :

Indication for Termination :

Chief Complaints :

Menstrual History :

Marital History :

Obstetric History :

Past History :

Personal History :

Family History :

O/E : Wt BP Pallor

Ht PR Edema

INVESTIGATIONS :

Hb

PCV

Blood Grouping and Typing

USG OBSTERTRICS :

IU , GA

P/A :

P/S :

P/V , Cx Length : Mifepristone :

OS : Time :

Dose :

Misoprostol :

Isosorbide Mononitrate :

No. of Doses :

Time of Expulsion :

Induction Abortion Interval :

Completeness :

Side Effects : **ISMN added Groups** :

Vomitting : Headache :

Fever : Palpitation :

Shivering : Tachycardia :

Diarrhoea : Hypotension :

Abdominal Pain : Dizziness :

Antibiotics:

Any Operative Intervention :

Post Op Follow Up :

MASTER CHART

S.No.	NAME	AGE (Yrs)	GA (Weeks)	GRAVIDITY	INDICATION	USG	DOSES OF ISMN, MISO	TOTAL DOSE		INTERVAL	COMPLETE INCOMPLETE
								MISO (µg)	ISMN (mg)		
1	Shanthi	22	16w2d	Primi	Anomalous	18 w5 d	3	1200	80	10.5	C
2	Devi	24	14w	G2P1L1	Anomalous	14w2d	2	800	60	6	C
3	Vijaya	25	20w	G2P1L1	Severe Oligo	20 w	2	800	60	6.2	C
4	Valarmathy	19	13w3d	Primi	Medical	12w3d	2	800	60	5.4	C
5	Arokiyamal	19	19w	Primi	PPROM	19w	2	800	60	6	C
6	Leelavathi	24	13w	Primi	Social	13w	4	1600	100	14	C
7	Uma	26	16w5d	G3P2L2	Cont Fail	18w	1	400	40	2.2	C
8	Mary Florence	22	12w4d	G2P1L1	Missed AB	13w	2	800	60	5	C
9	Priya	21	14w2d	G2A1	Missed AB	14w	1	400	40	3.3	I
10	Khurshed Banu	20	20w	Primi	Social	19w2d	2	800	60	7	C
11	Anandi	30	17w	G2P1L1	Anomalous	18w	1	400	40	3	C
12	Rajeshwari	28	14w	G3P2L2	Social	14w2d	1	400	40	2.5	C
13	Noor Jahan	32	18w	Primi	IUFD	18w	3	1200	80	10	C
14	Amudha	25	20w	Primi	IUFD	19w6d	3	1200	80	11.3	C
15	Jayanthi	24	17w	Primi	Anomalous	17w	2	800	60	7	C
16	Revathy	22	184d	G2A1	Severe Oligo	18w	2	800	60	7.2	C
17	Bhuvaneshwari	30	20w	G4P2L2A1	Social	18w	1	400	40	3	C
18	Hussaina	29	14w2d	G2P1L1	Anomalous	14w	2	800	60	8	C
19	Manjula	32	17w	G3P2L2	Cont Fail	17w	2	800	60	5.4	C
20	Maya	28	12w6d	Primi	Medical	13w	3	1200	80	10	C
21	Pusphavalli	22	14w	Primi	Social	15w2d	2	800	60	7	C
22	Bhavani	25	13w3d	G4A3	IUFD	15w	2	800	60	6.3	C
23	Usha	18	14w	G5P2L2A2	Social	16w	1	400	40	2.3	C
24	Mary	23	16w3d	Primi	PPROM	17w	2	800	60	8.5	C
25	Ponni	24	17w	Primi	Anomalous	17w	3	1200	80	11	C
26	Manimala	19	17w	Primi	severe PIH	17w2d	2	800	60	9	C
27	Vimala	22	16w2d	Primi	Anomalous	15w	3	1200	80	12.5	C
28	Susheela	29	15w	G2P1L1	IUFD	15w	2	800	60	6	C
29	Kanchana	20	15w4d	G2P1L1	Anomalous	16w	2	800	60	8	C
30	Anitha	30	20w	G2P1L1	Anomalous	18w	2	800	60	7.3	C
31	Chithra	27	14w	G3P2L2	Social	20w	1	400	40	4	C
32	Komala	25	19w5d	G3A2	PPROM	20w	2	800	60	8.5	C
33	Megala	28	17w	G3P2L2	Cont Fail	16w4d	2	800	60	9	C
34	Maragatham	24	14w5d	G4P3L3A1	Social	14w	2	800	60	10.2	C

S.No.	NAME	AGE (Yrs)	GA (Weeks)	GRAVIDITY	INDICATION	USG	DOSES OF ISMN, MISO	TOTAL DOSE		INTERVAL	COMPLETE INCOMPLETE
								MISO (µg)	ISMN (mg)		
35	Subathra	26	15w	G3P2L2	Medical	15w	2	800	60	10	C
36	Rani	27	16w2d	Primi	Social	15w	3	1200	80	13	C
37	Selvi	31	17w	Primi	Anomalous	17w	3	1200	80	11	C
38	Sumalatha	22	20w	Primi	Anomalous	20w	4	1600	100	15	I
39	Kathayee	28	12w2d	Primi	Anomalous	13w	3	1200	80	12	C
40	Rahathi	20	13w	G4P2L1A1	Medical	13w3d	2	800	60	7	C
41	Mariam	25	15w	G2P1L2	Anomalous	15w	2	800	60	6	C
42	Uagarani	20	16w4d	Primi	severe PIH	15w5d	2	800	60	7	C
43	Parameshwari	18	17w	Primi	PPROM	17w	2	800	60	5	C
44	Gangavalli	22	17w	G4P3L3	Social	17w	1	400	40	3	C
45	Salma Bee	32	19w2d	Primi	IUFD	19w	3	1200	80	11	C
46	Rekha	27	12w4d	G2A1	IUFD	13w	2	800	60	7	I
47	Thenmozhi	18	15w	Primi	Social	14w	2	800	60	8	C
48	Kalaivani	24	16w	G3P2L2	Social	16w	1	400	40	2.5	C
49	Inbarasi	25	16w 2d	G4P3L3	Cont Fail	16w	1	400	40	3.2	C
50	Sankari	26	18w	G2A1	Anomalous	18 w5 d	2	800	60	6	C

S.No.	NAME	SIDE EFFECTS									INTERVENTION
		FEVER	SHIVERING	NAUSEA VOMITING	DIARRHOEA	ADB PAIN	HEADACHE	HYPOTENSION	TACHYCARDIA	RETAINED PLACENTA	
1	Shanthi	-	-	-	-	+	-	-	-	-	No
2	Devi	-	-	-	-	+	-	-	-	-	No
3	Vijaya	-	-	-	-	++	-	-	-	-	No
4	Valarmathy	-	-	-	-	+	-	-	-	-	No
5	Arokiyamal	-	-	-	-	-	-	-	-	-	No
6	Leelavathi	+	-	-	+	++	+	-	-	-	No
7	Uma	-	-	-	-	-	-	-	-	-	No
8	Mary Florence	-	-	-	-	+	-	-	-	-	No
9	Priya	-	-	-	-	-	-	-	-	+	Check Curretage
10	Khurshed Banu	-	-	-	-	+	-	-	-	-	No
11	Anandi	-	-	-	-	-	-	-	-	-	No
12	Rajeshwari	-	-	-	-	+	-	-	-	-	No
13	Noor Jahan	-	-	-	-	+	-	-	-	-	No
14	Amudha	-	-	-	-	-	-	-	-	-	No
15	Jayanthi	-	-	-	-	-	-	-	-	-	No
16	Revathy	-	-	-	-	-	-	-	-	-	No
17	Bhuvaneshwari	-	-	-	-	-	-	-	-	-	No
18	Hussaina	-	-	-	-	-	-	-	-	-	No
19	Manjula	-	-	-	-	-	-	-	-	-	No
20	Maya	-	-	-	-	-	-	-	-	-	No
21	Pusphavalli	-	-	-	-	-	-	-	-	-	No
22	Bhavani	-	-	-	-	+	-	-	-	-	No
23	Usha	-	-	-	-	-	-	-	-	-	No
24	Mary	-	-	-	-	-	-	-	-	-	No
25	Ponni	-	-	-	+	++	-	-	-	-	No
26	Manimala	-	-	-	-	+	-	-	-	-	No
27	Vimala	-	-	-	-	+	-	-	-	+	Check Curretage
28	Susheela	-	-	-	-	-	-	-	-	-	No
29	Kanchana	-	-	-	-	-	-	-	-	-	No
30	Anitha	-	-	-	-	-	-	-	-	-	No
31	Chithra	-	-	-	-	-	-	-	-	-	No
32	Komala	-	-	-	-	-	-	-	-	-	No
33	Megala	-	-	-	-	-	-	-	-	-	No
34	Maragatham	-	-	-	-	-	-	-	-	-	No

S.No.	NAME	SIDE EFFECTS									INTERVENTION
		FEVER	SHIVERING	NAUSEA VOMITING	DIARRHOEA	ADB PAIN	HEADACHE	HYPOTENSION	TACHYCARDIA	RETAINED PLACENTA	
35	Subathra	-	-	-	-	+	-	-	-	-	No
36	Rani	+	-	-	+	+	-	-	-	-	No
37	Selvi	-	-	-	-	++	-	-	-	+	Check Curretage
38	Sumalatha	+	+	-	-	++	+	-	-	-	No
39	Kathayee	-	-	-	-	+	-	-	-	-	No
40	Rahathi	-	-	-	-	-	-	-	-	-	No
41	Mariam	-	-	-	-	-	-	-	-	-	No
42	Uagarani	-	-	-	-	-	-	-	-	-	No
43	Parameshwari	-	-	-	-	-	-	-	-	-	No
44	Gangavalli	-	-	-	-	-	-	-	-	-	No
45	Salma Bee	-	-	-	-	+	-	-	-	-	No
46	Rekha	-	-	-	-	-	-	-	-	-	No
47	Thenmozhi	-	-	-	-	-	-	-	-	-	No
48	Kalaivani	-	-	-	-	-	-	-	-	-	No
49	Inbarasi	-	-	-	-	-	-	-	-	-	No
50	Sankari	-	-	-	-	-	-	-	-	-	No

TERMINATION WITH INTRAVAGINAL MISOPROSTOL - Group-B

S. No.	Name	AGE (Yrs)	GA (Weeks)	GRAVIDITY	INDICATION	USG	No. Doses of MISO	Dose of MISO	INTERVAL
1	Koteshwara	23	17	G2P1L1	Anomaly	17	2	800	9
2	Vijaya Lakshmi	29	14	Primi	Anomaly	14	3	1200	12.5
3	Rajini	23	19+2	Primi	Severe oligo	19	4	1600	18
4	Kumutha	24	15+3	Primi	IUFD	16	2	800	8
5	Reena	20	12+4	Primi	Medical	12+6	3	1200	13
6	Bagitha	23	16	Primi	Anomaly	16	3	1200	14.3
7	Sharanya	20	14	G4P3L3	Social	14+4	1	400	3
8	Kaviya	24	18+6	G4P2L2A1	Cont failure	18	2	800	7
9	Selvi	24	18+2	G3P2L2	Social	19	1	400	3.4
10	Panjali	33	13+3	G3P2L3	Social	14	2	800	6
11	Piraimathi	24	12+2	G4A3	Missed Ab	13+5	2	800	8
12	Sangeetha	27	18	G5P1L1A4	Medical	17	2	800	9.3
13	Sundari	28	18	Primi	Anomaly	17+5	3	1200	12.5
14	Lakshmi	29	16	Primi	Anomaly	16	3	1200	14
15	Rajeshwari	27	17+6	Primi	Severe PIH	19	4	1600	16
16	Chitra	26	20	G2P1L1	Severe oligo	20	2	800	9
17	Vijaya	19	16+4	G2P1L1	IUFD	16	2	800	10.4
18	Manimegalai	32	17	G2P1L1	IUFD	17	3	1200	14
19	Sudha	20	15	G3P1L1A1	Medical	14+3	2	800	9
20	Hemalatha	24	14	G2A1	Medical	14	2	800	10.2
21	Rani	31	17+2	G2A1	Anomaly	17	3	1200	13
22	Bhuvaneshwari	26	14+3	Primi	Social	14	4	1600	20
23	Saranya	23	18	Primi	IUFD	19+2	3	1200	15
24	Swathi	19	18	Primi	anomaly	18	3	1200	13
25	Nathiya	19	19+5	G3P2L2	Social	19	2	800	7
26	Maheshwari	27	20	G3P1L1A1	Medical	20	2	800	7

S. No.	Name	AGE (Yrs)	GA (Weeks)	GRAVIDITY	INDICATION	USG	No. Doses of MISO	Dose of MISO	INTERVAL
27	Sundari	27	19+1	G4P2L2A1	Cont failure	20	1	400	3
28	Sathya	19	14+6	Primi	Anomaly	14	2	800	5.4
29	Shabeena	20	13+2	Primi	Anomaly	13	3	1200	11.3
30	Sheela Devi	27	17	Primi	Anomaly	16+4	3	1200	11
31	Padma Priya	24	19+6	G3A2	PPROM	18	2	800	6
32	Bhavani	19	18+2	G2P1L1	Anomaly	17+3	2	800	6.3
33	Ezhilarasi	28	15+2	G2P1L1	Anomaly	15	2	800	5
34	Rose Mary	24	17	G2P1L1	Severe PIH	17	2	800	7
35	Gowri	25	20	G4A3	Severe oligo	20	1	400	2
36	Jaya Bharathi	30	19+5	Primi	Anomaly	19	3	1200	11
37	Mahalakshmi	25	12+4	Primi	Anomaly	12	2	800	9
38	Ambika	27	13+5	Primi	Social	14	4	1600	22
39	Dhanalakshmi	28	13	G3P2L2	Social	14	2	800	7.5
40	Priya	36	18	G3P2L2	Social	17+4	1	400	3
41	Bhavani	29	18+2	G3P2L2	Cont failure	20	2	800	9
42	Parameshwari	28	18	G5P3L3A1	Social	18	1	400	2
43	Menaka	29	20	G2P1L2	Social	19+5	3	1200	14
44	Balajothi	28	19+3	G2P1L1	Anomaly	19	2	800	10
45	Kuppu	20	19+6	G2P1L1	PPROM	19	2	800	10.4
46	Pattathurani	23	20	G2A1	IUFD	17	2	800	12
47	Bakiyalakshmi	19	12+4	Primi	Medical	12+3	3	1200	15
48	Amalarani	19	15	Primi	Anomaly	15	4	1600	18
49	Sumathi	27	12+6	G3P2L2	Social	13	2	800	9
50	Farzana	35	13+4	G4P2L2A1	Medical	13+5	1	400	3

S. No.	Name	COMPLETE INCOMPLETE	FEVER	SHIVERING	NAUSEA VOMITING	DIARRHOEA	ADB PAIN	RETAINED PLACENTA	INTERVENTION
1	Koteshwara	Complete	-	-	-	-	+	-	No
2	Vijaya Lakshmi	Complete	-	-	-	-	+	-	No
3	Rajini	Complete	+	-	-	-	+	-	No
4	Kumutha	Complete	-	-	-	-	-	-	No
5	Reena	Complete	-	-	-	-	-	-	No
6	Bagitha	Complete	+	-	-	-	-	-	No
7	Sharanya	Complete	-	-	-	-	-	-	No
8	Kaviya	Complete	-	-	-	-	-	-	No
9	Selvi	Complete	-	-	-	-	+	-	No
10	Panjali	Complete	-	-	-	-	+	-	No
11	Piraimathi	Complete	-	-	-	-	-	-	No
12	Sangeetha	Complete	-	-	-	-	+	-	No
13	Sundari	Incomplete	-	--	-	-	-	+	Check currette
14	Lakshmi	Complete	-	-	-	+	-	-	No
15	Rajeshwari	Incomplete	+		-	+	+	+	Check currette
16	Chitra	Complete	-	-	-	-	-	-	No
17	Vijaya	Complete	-	-	-	-	-	-	No
18	Manimegalai	Complete	-	-	-	-	+	-	No
19	Sudha	Complete	+	-	-	-	+	-	No
20	Hemalatha	Complete	-	-	-	-	+	-	No
21	Rani	Complete	-	-	-	-	+	-	No
22	Bhuvaneshwari	Incomplete	+	+	-	+	+	+	Check currette
23	Saranya	Complete	+	-	-	-	+	-	No
24	Swathi	Complete	-	-	-	-	+	-	No
25	Nathiya	Complete	-	-	-	-	+	-	No
26	Maheshwari	Complete	-	-	-	-	+	-	No

S. No.	Name	COMPLETE INCOMPLETE	FEVER	SHIVERING	NAUSEA VOMITING	DIARRHOEA	ADB PAIN	RETAINED PLACENTA	INTERVENTION
27	Sundari	Complete	-	-	-	-	+	-	No
28	Sathya	Complete	-	-	-	-	+	-	No
29	Shabeena	Complete	-	-	-	-	+	-	No
30	Sheela Devi	Complete	-	-	-	-	+	-	No
31	Padma Priya	Complete	-	-	-	-	+	-	No
32	Bhavani	Complete	-	-	-	-	+	-	No
33	Ezhilarasi	Complete	-	-	-	-	+	-	No
34	Rose Mary	Complete	-	-	-	-	+	-	No
35	Gowri	Complete	-	-	-	-	-	-	No
36	Jaya Bharathi	Incomplete	+	-	-	-	+	+	Check currette
37	Mahalakshmi	Complete	-	-	-	-	+	-	No
38	Ambika	Incomplete	-	-	-	+	+	+	Check currette
39	Dhanalakshmi	Complete	-	-	-	-	+	-	No
40	Priya	Complete	-	-	-	-	-	-	No
41	Bhavani	Complete	-	-	-	-	+	-	No
42	Parameshwari	Complete	-	-	-	-	+	-	No
43	Menaka	Complete	-	-	-	-	+	-	No
44	Balajothi	Complete	-	-	-	-	+	-	No
45	Kuppu	Complete	-	-	-	-	+	-	No
46	Pattathurani	Complete	-	-	-	-	+	-	No
47	Bakiyalakshmi	Complete	-	-	-	-	+	-	No
48	Amalarani	Complete	-	-	-	+	+	-	No
49	Sumathi	Complete	-	-	-	-	+	-	No
50	Farzana	Complete	-	-	-	-	+	-	No

@EJL 1284.4
@EJL

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.Rukkayal Fathima.P.
II Year PG in M.D.(Obstetrics & Gynaecology)
Inst. of Obstetrics and Gynaecology
Madras Medical College
Chennai 600 003

Dear Dr.Rukkayal Fathima.P.,

The Institutional Ethics Committee has considered your request and approved your study titled **"COMPARISON OF MISOPROSTOL AND MISOPROSTOL WITH ISOSORBIDE MONO NITRATE FOR SECOND TRIMESTER MEDICAL TERMINATION "** NO.05012015.

The following members of Ethics Committee were present in the meeting hold on 20.01.2015 conducted at Madras Medical College, Chennai 3.

1. Dr.C.Rajendran, MD	:Chairperson
2. Dr.R.Vimala,MD.,Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi,MD.,Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.R.Nandhini,MD.,Inst.of Pharmacology,MMC	: Member
5. Prof.P.Ragumani, MS., Professor, Inst.of Surgery,MMC	: Member
6. Prof.K.Ramadevi, Director , Inst.of Bio-Chem.MMC	: Member
7. Prof.Saraswathy,MD.,Director,Pathology, MMC	: Member
8. Prof.Md.Ali, MD., DM.,Prof.&HOD of Medl.GE,MD.MMC	: Member
9. Thiru S.Rameshkumar	: Lay Person
10.Thiru S.Govindasamy, BA., BL.,	: Lawyer
11.Tmt.Arnold Saulina, MA., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Sys 2

Member Secretary - Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

Information to Participants

Title : Comparison of Misoprostol and Misoprostol with Isosorbide Mononitrate for Second Trimester Medical Termination.

Principal Investigator : **Dr. Rukkayal Fathima**

Name of Participant :

Site : **IOG, Egmore, Chennai-8.**

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

To compare the effectiveness and safety profile of Misoprostol and Misoprostol with Isosorbide Mononitrate when used in second trimester medical termination.

We have obtained permission from the Institutional Ethics Committee.

The study design

All patients in the study will be divided into two groups. You will be assigned to either of the groups.

Study Procedures

The study involves a basic medical examination and routine blood examination. An ultrasound obstetrics is performed to diagnose the appropriate gestational age and confirm the diagnosis such as (Oligohydramnios / Congenital Anomanies).

Patients are allotted into two groups.

Group I - 600μg misoprostol kept per vaginally followed by 400μg of misoprostol every 4th hourly, maximum 5 doses.

Group II - 600μg misoprostol with 80mg of Isosorbide mononitrate kept per vaginally followed by 400μg misoprostol with 40mg of Isosorbide mononitrate every 4th hourly, maximum 5 doses.

The cumulative time for termination of pregnancy in each of the group and side effect profile of both the groups are analyzed.

Possible benefits to you

The cumulative time of termination of pregnancy and side effects such as abdominal pain and bleeding are reduced when misoprostol is used with isosorbide mononitrate

INFORMED CONSENT FORM

Title : Comparison of Misoprostol and Misoprostol with Isosorbide mononitrate for Second Trimester Medical Termination.

Name of the Investigator : **Dr. Rukkayal Fathima**

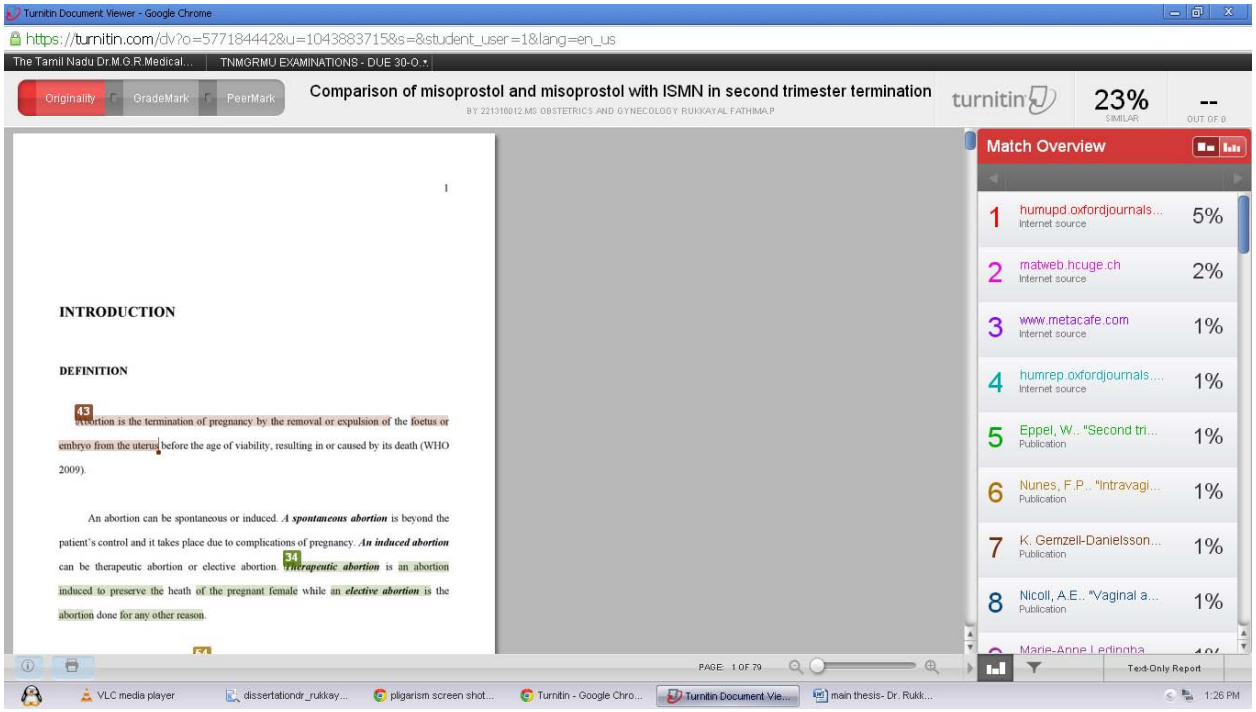
Name of the Participant :

Name of the Institution : IOG, Egmore, Chennai-8.

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have informed the investigator of all the treatments I am taking or have taken in the past months/years including any native (alternative) treatments.
6. I have been advised about the risks associated with my participation in the study.*
7. I agree to cooperate with the investigator and I will inform him /her immediately if I suffer unusual symptoms. *
8. I have not participated in any research study within the past _____ month(s). *
9. I have not donated blood within the past _____ months. (Add if the study involves extensive blood sampling). *
10. I am aware of the fact that I can opt out of the study at any time without having to give any reasoned this will not affect my future treatment in this hospital. *
11. I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent. *
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC if required.
13. I understand that my identity will be kept confidential if my data are publicly presented.
14. I have had my questions answered to my satisfaction.
15. I consent voluntarily to participate in the research/study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me. I will be given a copy of this consent document.

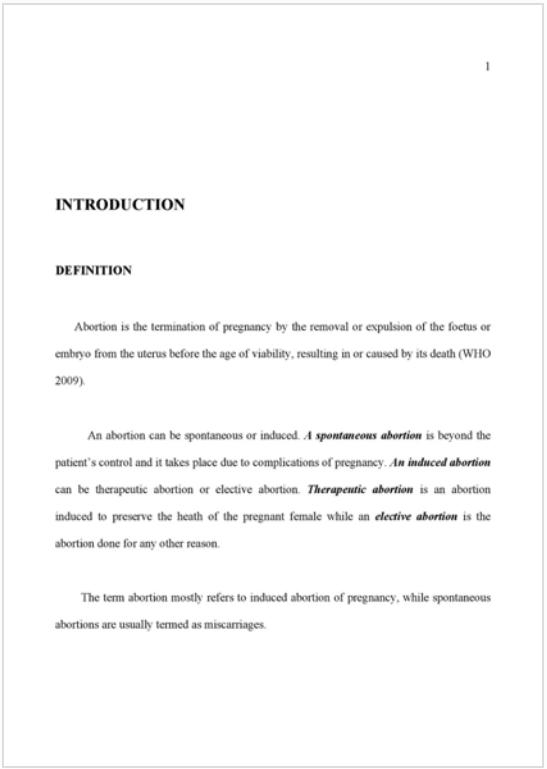

Turnitin Document Viewer - Google Chrome
https://turnitin.com/dv?o=577184442&u=1043883715&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 30-O...
Originality
GradeMark
PeerMark
Comparison of misoprostol and misoprostol with ISMN in second trimester termination
BY 221316012.MS OBSTETRICS AND GYNECOLOGY RUKKAYAL FATHIMA.P
turnitin
23%
SIMILAR
--
OUT OF 0
1
INTRODUCTION
DEFINITION
Abortion is the termination of pregnancy by the removal or expulsion of the foetus or embryo from the uterus before the age of viability, resulting in or caused by its death (WHO 2009).
An abortion can be spontaneous or induced. A spontaneous abortion is beyond the patient's control and it takes place due to complications of pregnancy. An induced abortion can be therapeutic abortion or elective abortion. Therapeutic abortion is an abortion induced to preserve the heath of the pregnant female while an elective abortion is the abortion done for any other reason.
Match Overview
1 humupd.oxfordjournals... Internet source 5%
2 matweb.hcuge.ch Internet source 2%
3 www.metacafe.com Internet source 1%
4 humrep.oxfordjournals.... Internet source 1%
5 Eppel, W.. "Second tri... Publication 1%
6 Nunes, F.P.. "Intravagi... Publication 1%
7 K. Gemzell-Danielsson... Publication 1%
8 Nicoll, A.E.. "Vaginal a... Publication 1%
PAGE: 1 OF 79
Text-Only Report
VLC media player
dissertationdr_rukkay...
pligarism screen shot...
Turnitin - Google Chro...
Turnitin Document Vie...
main thesis- Dr. Rukk...
1:26 PM

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	221316012.ms Obstetrics And Gyn...
Assignment title:	TNMGRMU EXAMINATIONS
Submission title:	Comparison of misoprostol and m...
File name:	edited_thesis.docx
File size:	50.45K
Page count:	79
Word count:	10,210
Character count:	54,980
Submission date:	01-Oct-2015 12:45PM
Submission ID:	577184442



1

INTRODUCTION

DEFINITION

Abortion is the termination of pregnancy by the removal or expulsion of the foetus or embryo from the uterus before the age of viability, resulting in or caused by its death (WHO 2009).

An abortion can be spontaneous or induced. ***A spontaneous abortion*** is beyond the patient's control and it takes place due to complications of pregnancy. ***An induced abortion*** can be therapeutic abortion or elective abortion. ***Therapeutic abortion*** is an abortion induced to preserve the heath of the pregnant female while an ***elective abortion*** is the abortion done for any other reason.

The term abortion mostly refers to induced abortion of pregnancy, while spontaneous abortions are usually termed as miscarriages.